Volume 100 Number 1

July 1980

American Heart Journal

An international publication for the study of the circulation

George E Burch *Editor*
James A Cronvich *Assistant Editor*
Peter C Gazes *Assistant Editor*

International Editorial Board

Walter H Abelmann *Boston Mass*
William B Abrams *West Point Pa*
David I Abramson *Oak Park Ill*
Raymond P Ahlquist *Augusta Ga*
James K Alexander *Houston Tex*
A C Arntzenius *Leiden The Netherlands*
John B Barlow *Johannesburg South Africa*
Giorgio Baroldi *Milan Italy*
Henry W Blackburn *Minneapolis Minn*
Thomas M Blake *Jackson Miss*
S Gilbert Blount Jr *Denver Colo*
Eugene Braunwald *Boston Mass*
Howard B Burchell *Minneapolis Minn*
E[illegible] I Chazov *Moscow USSR*
J[illegible] Chevalier *Paris France*
Te Chu[illegible] Chou *Cincinnati Ohio*
Ernest Cra[illegible]e *Chapel Hill N C*
Arthur C DeGraff *New York N Y*
H Denolin *Brussels Belgium*
James F Doherty *Little Rock Ark*
Jesse E Edwards *St Paul Minn*
Robert H Eich *Syracuse N Y*
Mary Allen Engle *New York N Y*
Ali M Fakhro *Manama Bahrain*
M Irené Ferrer *New York N Y*
Nancy C Flowers *Louisville Ky*
Nicholas J Fortuin *Baltimore Md*
Martin J Frank *Augusta Ga*
Edward D Freis *Washington D C*
Julian Frieden *New Rochelle N Y*
Meyer Friedman *San Francisco Cal*
Jacques Genest *Montreal Canada*
Allan V.N Goodyer *New Haven Conn*
Mervyn S Gotsman *Jerusalem Israel*
Joseph C Greenfield Jr *Durham N C*
Robert L. Grissom *Omaha Neb*
Dale Groom *Oklahoma City Okla*
Rolf M Gunnar *Chicago Ill*
Warren G Guntheroth *Seattle Wash*
F William Hancock *Stanford Cal*
Herbert N Hultgren *Palo Alto Cal*
Hiroo Ishikawa *Nara Japan*
Lewis E. Januari *Iowa City Iowa*
James N Karnegis *Minneapolis Minn*
John A Kastor *Philadelphia Pa*
Nodar N Kipshidze *Tbilisi USSR*
Henri E Kulbertus *Liège Belgium*
Richard Langendorf *Chicago Ill*
Jean Lequime *Brussels Belgium*
Maurice Lev *Chicago Ill*
Harold D Levine *Boston Mass*
R J Linden *Leeds England*
F Loogen *Dusseldorf Germany*
Hugh A McAllister Jr *Washington D C*
Dan G McNamara *Houston Tex*
George F Maha *West Point Pa*
Alberto Malliani *Milan Italy*
Bill L Martz *Indianapolis Ind*
Rashid A Massumi *Tehran Iran*
Clifford V Nelson *Portland Maine*
Satoshi Ohta *Tokyo Japan*
Eckhardt G J Olsen *London England*
Morton Lee Pearce *Los Angeles Cal*
Alfred Pick *Chicago Ill*
Hubert V Pipberger *Washington D C*
Walter H Pritchard *Cleveland Ohio*
Ray Pryor *Denver Colo*
William Roberts *Bethesda Md*
Robert C Schlant *Atlanta Ga*
H A Snellen *Leiden The Netherlands*
Walter Somerville *London England*
John Thomas *Nashville Tenn*
Hironori Toshima *Kyushu Japan*
William H Wehrmacher *Chicago Ill*
Hein J J Wellens *Maastricht The Netherlands*
Alberto Zanchetti *Milan Italy*
Douglas P Zipes *Ind*

1 1980 please submit
to
on M D
Cardiovascular
y of California
Medicine
lifornia 95616

To prevent predictable angina*

ED. ROBERT HEALTH LIBRARY
SGM
Ace N 76366
Date 95

CHEWABLE SORBITRATE®

(ISOSORBIDE DINITRATE) 5 mg or 10 mg

endable, prolonged protection during periods of emotional or physical exertion

ary Of Prescribing Information

tions: Based on review of this drug by The nal Academy of Sciences—National Research Council and/or other information, FDA has classified the indications as follows:
robably effective: The chewable dosage form of SORBITRATE is indicated for the treatment of anginal attacks and for prophylaxis in situations likely to provoke such attacks.
nal classification of the less than effective indications requires further investigation.

ndications: A history of sensitivity to the drug
ngs: Data supporting the use of nitrates during the acute phase of myocardial infarction are insufficient to establish safety.
tions: Tolerance and cross tolerance to other nitrates may occur.

Adverse Reactions. Headache which may be severe and persistent. Lowering the dose and using analgesics will help control the headaches which usually diminish or disappear as therapy is continued.

Adverse reactions seen occasionally: Cutaneous vasodilation with flushing; transient dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypotension; individual marked sensitivity to the hypotensive effects of nitrates wherein severe responses can occur even with the usual therapeutic dose (alcohol may enhance this effect); drug rash and/or exfoliative dermatitis.

This drug can act as a physiological antagonist to norepinephrine, acetylcholine, histamine and other agents.

Dosage and Administration: Individual Dose: To minimize hypotensive responses, which may occasionally be severe with chewable doses as low as 5 mg, the smallest effective dose should be employed. Chewable tablets are generally given in doses of 5 mg.

Dosage Schedule: Smallest effective dose necessary for the prevention and treatment of pain of an angina attack. CHEWABLE SORBITRATE (isosorbide dinitrate) may be taken for prompt relief of anginal pain three or four times daily. Although the onset and duration of effect of coronary nitrates may vary, following is the generally reported range of these values for CHEWABLE SORBITRATE.

Onset of Effect: Two to five minutes.
Duration of Effect: One to two hours.



STUART PHARMACEUTICALS
Division of ICI Americas Inc
Wilmington, DE 19897

American Heart Journal

Contents

continued on page 7

Vol 100 No 1 July 1980 The American Heart Journal is published monthly by The C. V. Mosby Company 11830 Westline Industrial Drive St. Louis, Mo 63141

1980 Annual subscription rates	U.S.A.	Foreign countries (surface mail) All regions	Foreign countries (airmail) Region 1	Region 2	Region 3
Institutional†	$45.00	[illegible]	$67	$81.60	$95.65
Individuals‡	$[illegible]8.00	$39.00	$ 05	$64.60	$ 8.65
Student resident‡	$2 .40	$2 .40	$44.9	$ 9.00	$73.05

Single copies are $4.50 postpaid. Remittances should be made by check, draft, post office or express money order payable to this Journal.

Airmail breakdown—*Domestic* First-class and Priority rates for the U.S. and possessions are available upon request. *Region 1* Central America, islands and mainland colonies of European countries in The Americas. *Region 2* South America, Europe, Egypt, Africa (bordering the Mediterranean). *Region 3* Asia, Australia, Africa (other than Mediterranean), Middle East, Far East, The Pacific, U.S.S.R. (and constituent Republics).

†Institutional (multiple reader) subscriptions are available to public and private libraries, schools, hospitals and clinics, city, county, state, provincial and national government bureaus and departments and all commercial and private institutions and organizations.

‡Personal subscriptions and all student rate subscriptions must be in the names of, billed to, and paid by individuals. All student rate requests must indicate training status and name of institution.

Subscriptions may begin at any time.

Second class postage paid at St. Louis, Mo. and additional mailing offices.

Printed in the U.S.A. copyright © 1980 by The C. V. Mosby Company

"cardiac separation"...

Although over 80% of post ... patients can resume ... marital sexual activity ... of anginal pain often results in "cardiac separation" between patients and their families.

You can help minimize "cardiac separation" with a program of counseling and often with a prescription for Cardilate® (erythrityl tetranitrate).

Cardilate® increases exercise tolerance, helps patients return to more normal levels of activity—*including sexual activity.* Sublingually, Cardilate begins to work within 5 minutes, eliminating or reducing frequency and severity of anginal pain for up to 2 hours.

counsel & Cardilate®
(erythrityl tetranitrate)

CARDILATE® (ERYTHRITYL TETRANITRATE)

INDICATIONS Cardilate (Erythrityl Tetranitrate) ... ndicated for the prophylaxis and long term treatment of patient with frequent or recurrent anginal pain and ... associated with angina pectoris rather than for the treatment of the acute attack of angina ... onset is somewhat slower than that of nitroglycerin.

CONTRAINDICATIONS *Idiosyncrasy to this drug.*

WARNING Data supporting the use of nitrates du... the acute phase of myocardial infarction (the period during which clinical and laboratory findin... table) e... sufficient to establish safety.

PRECAUTIONS Intraocular pressure is increased ... required in administering to patients with glaucoma. Tolerance to this drug and cross toler... other ... tes and nitrates may occur.

ADVERSE REACTIONS Cutaneous vasodilation with ... g ... adache is common and may be severe and persistent. *Transient episodes of dizziness and weakness* ... the ... s of cerebral ischemia associated with ... ionally develop. *This drug can act* ... ological antagonist to norepinephrine ... marked sensitivity to the ... tion and collapse can occur even with the usual therapeutic dose. Alcohol may enhance this effect. Drug rash and/or exfoliative dermatitis may occasionally occur.

DOSAGE AND ADMINISTRATION

Oral Sublingual Tablets: Cardilate (Erythrityl Tetranitrate) may be administered either sublingually or orally. Therapy may be initiated with 10 mg prior to each anticipated physical or emotional stress and at bedtime for patients subject to nocturnal attacks. *The dose may be increased or decreased as needed.*

HOW SUPPLIED

CARDILATE (Erythrityl Tetranitrate) TABLETS (Scored) for ORAL or SUBLINGUAL USE 5 mg Bottle of 100; 10 mg Bottles of 100 and 1000; 15 mg Bottle of 100

Reference: 1. Hellerstein HK, Friedman EH: Sexual activity and the postcoronary patient. Arch Intern Med 125:98 ... 19 0

Burroughs Wellcome Co

... North Carolina 27709



Contents *continued*

continued on page



's more than enough to pay for your new cardiograph

Make your purchase before August 1 1980 and include enough Burdick ECG supplies to produce 150 rocardiograms And if you charge $20 00 per ECG means $3 000 potential income more than enough to the cost of the EK 8

The Burdick EK 8 is fully automatic requires only econds to record a complete 12 lead ECG And the is ready for immediate mounting on Burdick's self mounts A time saver and much more And now 'a with everything it needs to pay for itself Take advantage of this special offer Mail this or call toll free today 800-356 0701 (In Wis call 7631)

BURDICK

The Burdick Corporation
Milton Wisconsin 53563

Tell me more about your EK 8 REWARD offer

Name________________________

Address______________________ M D

City__________ State__________ Zip__________

Contents *continued*

(Information for authors on page 17)

(Index to advertisers on page 29)

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients. This consent is given on the condition however that the copier pay the stated per copy fee through the Copyright Clearance Center Inc 21 Congress St., Salem Mass. 01970 617 744 3350 for copying beyond that permitted by Sections 107 or 108 of the U S Copyright Law. This consent does not extend to other kinds of copying such as copying for general distribution for advertising or promotional purposes for creating new collective works or for resale

DOPSCAN®

The noninvasive, ultrasonic, stroke screening system to evaluate the carotid bifurcations

Color spectrum analyzer is available.

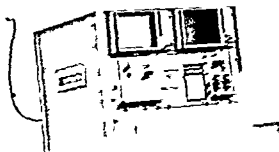
DOPSCAN® is a Doppler arterial scanning system for early detection of potential stroke conditions

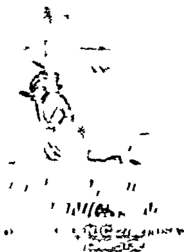
It provides a noninvasive evaluation of the carotid bifurcations and other peripheral arteries to indicate the location and severity of arterial insufficiency and plaquing It is a valuable supplement to X-ray angiography

DOPSCAN® provides a set of permanent exam records (1) Magnetic tape recordings of the Doppler flow sounds with the flow information in aural form along with the operator's commentary (2) Strip chart recordings showing pulsatile velocity waveforms and flow direction, and (3) Mapped images of the carotid bifurcations

An optional Sonascope™ Spectrum Analyzer designed specifically for the DOPSCAN® provides a color and real time display of the Doppler flow signals It separates arterial and venous flows and displays both simultaneously

™ Trademark of Carolina Medical Electronics Inc







PERSONALIZED LIBRARY CASES

Keep your personal copies of AMERICAN HEART JOURNAL in these specially designed library file cases Each file holds an entire year's issues Designed to keep your journal copies near at hand in your office library or home

Your case is heavy bookbinder's board in a rich red Kivar cover Files are scuff-resistant and washable

Lettering is stamped in gold leaf and the cases make a fit companion for the most costly binding

Files are reasonably priced—only $4 95 each, postpaid (3 for $14 6 for $24) Add $1 00 postage per case for orders outside U S Satisfaction unconditionally guaranteed or your money back! Use the coupon for prompt shipment.

Jesse Jones Box Corporation (est. 1843)
P O Box 5120
Philadelphia, Pa. 19141

Please send me postpaid ____ library cases for AMERICAN HEART JOURNAL at $4.95 each (3/$14, 6/$24.)

Name ______________________

Address ______________________

City ____________ State ____________ Zip ________

August 1980

American Heart Journal

Copyright © 1980 by The C V Mosby Company

Contents

continued on page 7

Vol. 100 No 2, August, 1980 The American Heart Journal is published monthly by The C V Mosby Company 11830 Westline Industrial Drive St. Louis Mo 63141

1980 Annual subscription rates	*U.S.A*	*Foreign countries (surface mail) All regions*	*Foreign countries (airmail) Region 1*	*Region 2*	*Region 3*
Institutional†	$45 00	$5[illegible] 00	$6[illegible].55	$[illegible]1 60	$95 6[illegible]
Individual‡	$[illegible]8 00	$38 00	$50.5[illegible]	$64 60	$78 65
Student resident‡	$22 40	$32.40	$44.95	$59 00	$73 05

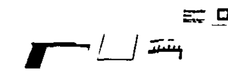
Single copies are $4.50 postpaid. Remittances should be made by check, draft, post office or express money order payable to this Journal.

Airmail breakdown—*Domestic* First-class and Priority rates for the U S and possessions are available upon request, *Region 1* Central America, islands, and mainland colonies of European countries in The Americas. *Region 2* South America, Europe Egypt Africa (bordering the Mediterranean) *Region 3* Asia, Australia Africa (other than Mediterranean) Middle East, Far East The Pacific U.S.S.R. (and constituent Republics)

†*Institutional (multiple reader)* subscriptions are available to public and private libraries schools, hospitals, and clinics city county state provincial and national government bureaus and *departments* and all commercial and private institutions and *organizations*.

‡Personal subscriptions and all student rate subscriptions must be *in the names of billed to and paid* by individuals. All student rate requests must indicate training status and name of institution. Subscriptions may begin at any time













Contents *continued*

(Information for authors on page 17)

(Index to advertisers on page 45)

The appearance of a ode at th bottom of the first page of n original article in this journal indicates the copyri ht owner s consent that copies of the article m y be made for personal o internal use or for th personal or internal use of specific clients. This consent i given on the condition howe er that the copier pay th stated per copy fee through the Copyright Cle rance Center Inc., ?1 Congress St., Salem Mass. 019 0 61 744-3450 for copying beyond that permitted by Sections 10 or 108 of the U S Copyright Law This c nsent does not e tend to oth r kind of copyi g such as copying for general distribution, for ad ertising or p omotional purp ses f r creating new collective works, or for resal



The North American Society of Pacing and Electrophysiology Young Investigators' Award For 1981

1st prize $1000 00 2nd prize $500 00
Honorable Mention $250 00

The North American Society of Pacing and Electrophysiology (NASPE) invites submission of manuscripts for competitive review and eventual presentation of the 1st and 2nd prize winning papers at its 2nd Annual Scientific Symposium on March 14th 1981 in San Francisco California The goal of this award is to encourage and give recognition to able young investigators for original investigation or basic research in the area of Cardiac Pacing and/or Cardiac Electrophysiology

ELIGIBILITY

Any physician or scientist who is presently involved in an active fellowship or residency program or who has been involved within the past three years is eligible to participate This includes medical students and PhD candidates Applicants must reside within or have received their academic training within the geographic boundaries of North America *

DEADLINE FOR SUBMISSION OF MANUSCRIPTS DECEMBER 15 1980

RULES

1 The investigation upon which the manuscript is based must be an original piece of investigation performed predominantly by the first author
2 The applicant must attest that the investigation has not previously been reported or published elsewhere and that if chosen by the judges as a prize winning entry will not be presented or published prior to March 14 1981
3 Award winning manuscripts will be published in PACE The Journal of Pacing and Electrophysiology
4 Abstracts of non award winning manuscripts deemed by the judges to be of high reader interest will also be published in PACE
5 Authors of award winning manuscripts are expected to attend the 2nd Annual Scientific Program of NASPE both for presentation of a 15 minute summary of their manuscript (1st and 2nd prize only) and receipt of awards

FOR APPLICATION FORMS AND FURTHER INFORMATION CONTACT

Dr Seymour Furman
Program Chairman
2nd Annual Scientific Program
NASPE
c/o Montefiore Hospital
111 East 210th Street
Bronx NY 10467

Support for this Award has been provided by a Professional Education Grant by Medtronic Inc

Canada United States Greenland Mexico Central America Carib-

EDITORS! REVIEWERS! AUTHORS!

For you a new book that contains virtually everything you want to know about

THE SCIENTIFIC JOURNAL EDITORIAL POLICIES AND PRACTICES

Guidelines for Editors, Reviewers, and Authors

In 1665 the first scholarly journal was published in France Since that time there has been no one source of editorial guidelines for journal editors This new book now provides you with such a source

YOU DECIDE YOUR OWN APPROACH!

Presenting the advantages and disadvantages of each specific decision eminent editors offer you various recommendations discussions and opinions concerning the problems you may encounter

Because we are aware that there is no right policy on most editorial matters we have tried not to prescribe rules but have instead explored various facets of the problems that confront the editor in his daily work

The book is divided into two general sections editorial policies which usually require major decisions and editorial practices which involve minor decisions often about format or mechanical style You ll find essays exploring the manuscript reviewing system special types of manuscripts (abstracts transactions solicited manuscripts book reviews) You ll value chapters which cover information for authors copyright, errata references cited copy editing journal cover etc

From the purpose of scientific journals to binding practices this new book contains virtually everything you want to know as editor reviewer or author See for yourself!

By Lois DeBakey Ph.D In collaboration with Paul F Cranefield, M D Ph D Ayodhya P Gupta M.D Franz J Ingelfinger M.D Robert J Levine M.D Robert H. Moser M.D J Roger Porter Ph D and F Peter Woodford, Ph D August, 1976 128 pages 6 × 9" Price $12.50

Please send me on 30-day approval THE SCIENTIFIC JOURNAL EDITORIAL POLICIES AND PRACTICES
Price $12.50
☐ Bill me ☐ Master Charge #______
☐ Payment enclosed

Name ______

Address ______

City ______

State ______ Zip Code ______

MOSBY
TIMES MIRROR

30-day approval offer good only in

American Heart Journal

Copyright © 1980 by The C V Mosby Company

Contents

continued on page 7

Vol. 100 No 3 September 1980 The American Heart Journal is published monthly by The C V Mosby Company 11830 Westline Industrial Drive St Louis, Mo 63141 POSTMASTER Send address change to above address

1980 Annual subscription rates	*U.S.A*	*Foreign countries (surface mail) All regions*	*Region 1*	*Foreign countries (airmail) Region 2*	*Region 3*
Institutional†	$45 00	$55 00	$67 55	$81 60	$9 65
Individual‡	$_8 00	$38 00	$50 55	$64 60	$ 8 65
Student resident‡	$[illegible] 40	$3_40	$44.95	$59 00	$ 3 05

Single copies are $4 50 postpaid Remittances should be made by check, draft post office or express money order payable to this Journal

Airmail breakdown—*Domestic* First class and Priority rates for the U S and possessions are available upon request *Region 1* Central America islands and mainland colonies of European countries in The Americas. *Region 2* South America Europe Egypt Africa (bordering the Mediterranean) *Region 3* Asia Australia Africa (other than Mediterranean) Middle East Far East The Pacific U.S.S.R. (and constituent Republics)

†Institutional (multiple-reader) subscriptions are available to public and private libraries schools, hospitals, and clinics city county state provincial and national government bureaus and department and all commercial and private institutions and organizations.

‡Personal subscriptions and all student rate subscriptions must be in the names of billed to and paid by individuals All student rate requests must indicate training status and name of institution

Subscriptions may begin at any time

Second class postage paid at St Louis Mo and additional mailing office

Printed in the U S A copyright © 1980 by The C V Mosby Company

for "cardiac separation"...



Although over 80% of post coronary patients can resume normal marital sexual activity fear of anginal pain often results in cardiac separation between patients and their families

You can help minimize "cardiac separation" with a program of counseling and often with a prescription for Cardilate (erythrityl tetranitrate)

Cardilate increases exercise tolerance helps patients return to *more normal levels of activity—* including sexual activity

Sublingually Cardilate begins to work within 5 minutes, eliminating or reducing frequency and severity of anginal pain for up to 2 hours

counsel & Cardilate®
(erythrityl tetranitrate)

CARDILATE ...

INDICATIONS ...

CONTRAINDICATIONS ...

WARNING ...

PRECAUTIONS ...

ADVERSE REACTION ...

DOSAGE AND ADMINISTRATION ...

HOW SUPPLIED

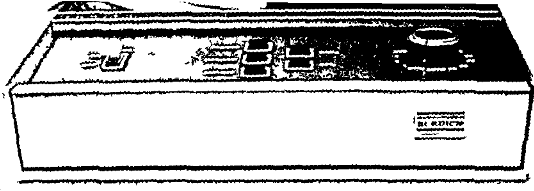
CARDILATE ...

Burroughs Wellcome Co
Research Triangle Park North Carolina 27709

ONE HUNDRED YEARS WELLCOME

Contents *continued*

continued on page 9



If you think the EK-8 is a fast recorder, see how it saves mounting time!

You know the Burdick EK 8 ..s a complete 12 lead ECG ..tomatically ... in less than ..3 seconds

That s impressive in a ..ngle channel cardiograph

But there s another important ..art to the EK 8 story

The EK 8 was designed to ..ve physician and staff time And ..ile it makes good sense to save ..e recording the ECG think of ..e additional time saving benefits ..hen you can mount and fil.. the ..CG in less time than it take.. ..cord the 12 lead tracing

That s why the EK 8 fast mounting system is important to you The answer is in our unique card and folder format mounts When the ECG is recorded the *technician takes the complete* tracing with each lead already clearly marked and quickly positions it on the pressure sensitive card or folder format mount No die cutting No pasting or taping It s *ready for filing* It can take less than a minute to record *and* mount the ECG

The Burdick mounting system Because the ECG isn t complete until the paperwork s done

Find out how the EK 8 can increase your ECG productivity from start to finish Call or write **The Burdick Corporation** ***Milton Wisconsin 53563***



Toll free 800 356 0701
In Wisconsin 608 868 763..

BURDICK

..concern for cardiac car..

Contents continued

(Information for authors on page 17)

(Index to advertisers on page 56)

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use, or for the personal or internal use of specific clients. This consent is given on the condition, however, that the copier pay the stated per copy fee through the Copyright Clearance Center, Inc., 21 Congress St., Salem, Mass. 01970 (617-744-3350) for copying beyond that permitted by Sections 107 or 108 of the U.S. Copyright Law. This consent does not extend to other kinds of copying, such as copying for general distribution, for advertising or promotional purposes, for creating new collective works, or for resale.

Optimum patient care. . .
maintain it with these Mosby references.

lew 4th Edition! **THE HUMAN HEART**
, Guide to Heart Disease By Brendan
hibbs MD F.A.C.P., F.A.C.C. with 5
ontributors A simple and practical guide
overing many aspects of heart disease,
his new 4th edition succinctly explains the
natomy,physiology and common diseases
f the heart. Information on drugs
mergency resuscitation,
atheterization and heart surgery
s well illustrated and provides an
xcellent reference for you - and
our staff August, 1979 288 pp
80 illus Price $13 95

lew 4th Edition! **COMPREHENSIVE**
CARDIAC CARE. A Text for Nurses
Physicians and Other Health
Practitioners By Kathleen G
Andreoli, R.N B.S.N. M.S.N
Virginia Hunn Fowkes, R.N B.S.N
Douglas P Zipes M.D and Andrew
J Wallace M.D This new edition
will give you the information on
all aspects of cardiac care -
anatomy and physiology- coronary
artery disease assessment of patients
complications electrocardiography- and
pacemakers New material covers risk factors
in coronary artery disease- interview physical
examination, and common laboratory
for patients with coronary
artery disease- and current
pacemaker therapy March, 1979
406 pp 699 illus. Price $12.50

CLINICAL ECHOCARDIOGRAPHY
By Navin C. Nanda M.D and
Raymond Gramiak, M.D This clinically-
oriented text is an excellent guide to
applying echocardiographic techniques in patient
evaluation. The authors first describe pertinent
physics, equipment, and recording methods and
review cardiac anatomy electrocardiography
phonocardiography and hemodynamics in relation to the performance and
interpretation of echocardiograms Section two discusses echo exam
techniques and skill acquisition. Throughout, emphasis is on technical
proficiency and interpretive expertise. 1978 468 pp 666 illus
Price $41.50

4th Edition **BLADES' SURGICAL DISEASES OF THE CHEST**
Edited by Donald Brian Effler M.D with 33 contributors. The 4th
edition of this widely respected volume presents the latest
developments in thoracic and cardiovascular surgery Throughout,
you'll share the viewpoints and experience of more than 30 contributors
— many new to this revision — all recognized authorities in their
respective fields. A particularly noteworthy chapter by Kazi Mobin-Uddin
discusses the surgical aspects of thromboembolism. 1978 856 pp
939 illus. Price, $65 00

New 2nd Edition! **MYOCARDIAL INFARCTION.**
Electrocardiographic Differential Diagnosis By Ary Louis
Goldberger M.D The 2nd edition of this unique reference extensively
details all major conditions that cause ECG changes which mimic
infarction patterns. It offers guidelines to help you differentiate
between actual and pseudo-infarct patterns and aids in diagnosis.
Three new chapters highlight this edition.
All deal with various aspects of
ST-depression, ischemic causes normal
variant and non-ischemic causes and false
positive exercise tests April, 1979
296 pp 336 illus Price, $27.50

New 2nd Edition! **CARDIOVASCULAR NUCLEAR MEDICINE.** Edited by H.
William Strauss M.D and Bertram Pitt,
M.D with 41 contributors An authoritative
overview of cardiovascular nuclear
medicine this revised and updated 2nd
edition presents not only the latest
techniques but also historical and
background information on the state of the
art. Of particular importance are two new
chapters Computer methods in nuclear
cardiology by David Lieberman and
Emission computed tomography of the
myocardium by John Keyes.
September 1979 442 pp
693 illus plus 4 in
full color Price $47.50

A New Book! **ISCHEMIC HEART DISEASE.** By I.K
Shkhvatsabaya Translated
by V.N. Bobrov and G S Vats
Don't miss this important
contribution to international medical
literature from Russia It discusses
some problems of ischemic heart disease
on the basis of experimental epidemiological and clinical
investigations conducted at The Myasnikov Institute of
Cardiology in the U S S R. Chapters detail the epidemiology
pathogenesis diagnostics management, rehabilitation and prevention
of ischemic heart disease June 1979 423 pp 123 illus Price $37.50

A New Book! **THE CARDIAC CYCLE.** By M.I.M. Noble Ph D M.D
F.R.C.S Based on the work of some of the world's leading investigators,
this new book reviews the latest ideas on the events in the cardiac cycle
from the pacemaker to the peripheral pulse Some of the theories
introduced by the authors are experimental and have yet to be proven
by critical test. Major sections of the book include the electrical cardiac
cycle the calcium cardiac cycle mechanism of contraction, and control
of the cardiac contractile performance. December 1979 Approx. 224
pp 90 illus About $38 75

CALL US! Dial toll free **(800) 325-4177 ext. 10** in Missouri, call
collect (314) 872-8370 ext. 10 during our regular business hours.
AMS105

MOSBY
TIMES MIRROR

THE C V MOSBY COMPANY
11830 WESTLINE INDUSTRIAL DRIVE
ST LOUIS MISSOURI 63141

American Heart Journal

Copyright © 1980 by The C V Mosby Company

Contents

continued on page 7

Vol. 100 No 4 October 1980 The American Heart Journal is published monthly by The C. V Mosby Company 11830 Westline Industrial Drive St. Louis, Mo 63141 POSTMASTER Send address change to above address.

1980 Annual subscription rates	*U.S.A*	*Foreign countries (surface mail) All regions*	*Foreign countries (airmail) Region 1*	*Region 2*	*Region 3*
Institutional†	$45 00	$55 00	$67.55	$81 60	$95 65
Individual‡	$[illegible]8 00	$38 00	$[illegible]0 55	$64 60	$ [illegible]8 65
Student resident‡	$22.40	$3[illegible].40	$44.95	$[illegible]9 00	$73 05

Single copies are $4 50 postpaid Remittances should be made by check draft, post office or express money order payable to this Journal.

Airmail breakdown—*Domestic* First-class and Priority rates for the U.S and possessions are available upon request *Region 1* Central America, islands and mainland colonies of European countries in The Americas. *Region 2* *South America Europe Egypt Africa* (bordering the Mediterranean) *Region 3* Asia Australia Africa (other than Mediterranean) Middle East Far East, The Pacific U.S.S.R. (and constituent Republics)

†Institutional (multiple-reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics city county state provincial and national government bureaus and departments and all commercial and private institutions and organizations.

‡Personal subscriptions and all student rate subscriptions must be in the names of billed to and paid by individuals All student rate requests must indicate training status and name of institution

Subscriptions may begin at any time

Second class postage paid at St. Louis Mo and additional mailing offices.

Printed in the U.S.A copyright © 1980 by The C V Mosby Company

Remember

ZYLOPRIM®

the original (allopurinol)

100 and 300 mg

Scored Tablets

The name
Zyloprim
is now
imprinted on
each tablet

ZYLOPRIM

ZYLO



Burroughs Wellcome Co
Research Triangle Park
North Carolina 27709

Contents *continued*

continued on page 9

press of a finger
ves two problems

for the physician
more precise dosage titration

for the patient
easier compliance with
your dosage adjustments

ISORDIL TITRADOSE

(ISOSORBIDE DINITRATE) (E Z SPLIT*†) Oral Tablets 5 mg 10 mg 20 mg, and 30 mg

NOW...for greater
venience
compliance
in the higher spectrum
of the recommended
range

30 mg
ISORDIL TITRADOSE
(ISOSORBIDE DINITRATE) Tablets



Tablet show

*Indications Based on a review of th s dr g by the National Academy of Sciences—National Research Council and/or other inf rmation FDA has class fied th ind cations as follows
Possibly effective When taken by the oral route Isordil is indicated for th relief of a gina pectoris (pain of coronary artery disease) It is not intended to abort the acute anginal episode but is widely regarded as use ul in the pro hylactic treatment of angina pectoris
Final cla sif cation of th less than-effective i dications requires further investigation.

Contraindication Idiosyncrasy to this drug

Warnings Data s pporting the use of nitrites and nitrates during the early days of th acut phase of myocardial infarction (the period during which cl n ical and laboratory findi gs are unstabl) are in ufficient to establish safe y

Precautions Tolerance to this drug and cross tolerance to other nitrites and nitrates may occur

Adverse Reactions Cutaneous vasod lation with flushing Heada he is com mon and may be severe and persistent. Trans ent episod s of dizziness and weakness as well as other signs of cerebral ischemia associated with postural hypoten ion may occas onally develop This drug can act as a phys ol gical a tagon t to norepinephrine acetylcholine histamine and many other agents An occasional individual exhibits marked sensitivity to the hypotensive effects of nitrite and severe responses (nausea vom g w akness rest essn ss pallor perspiration and collapse) can occur even with the us al therapeutic dose Alcohol may enhance this effect. Drug rash and/or exfoliative dermat tis may occasiona ly occur

Dosage and Administration: Isord l (Isosorbid Dinitrate) Oral Titradose Tabl ts are administered orally The dosage range is 5 mg to 30 mg q i d with the usual dosage bei g 10 mg to 20 mg q i d

Consult direction circular before prescribing.

IVES LABORATORIES INC
New York NY 10017
DEDICATED TO IMPRO NG THE QUALITY OF LIFE THROUGH MEDICINE®

US Pat 1 os ?? 3647 and ?224 ?

Contents *continued*

continued on page II

Contents *continued*

(Information for authors on page 19)

(Index to advertisers on page 40)

The appearance of a code at the bottom of the first pag of an original article in this journal indicates th copyright owner s consent that copies of the article m y be made f r person l or internal use or for the personal or internal use of spec fic cli nts. This consent is giv n on the cond tion, however that th copier pay the stated per copy fee through the Copyright Clearance Center Inc 21 Congress St Salem, Mass. 01970 617 744-3350 for copying beyond that permitted by Sections 107 or 108 of the U S Copyright Law This consent does not e t nd to other k nds of copying such as copying for general distribution for ad ertising or promotional purposes, for reating new collect ve w rks, o for resale

American Heart Journal

Copyright © 1980 by The C V Mosby Company

Contents

continued on page 7

Vol. 100 No 5 November 1980 The American Heart Journal is published monthly by The C V Mosby Company 11830 Westline Industrial Drive St. Louis Mo 63141 POSTMASTER Send address change to above address

1981 Annual subscription rates	*U.S.A*	*Foreign countries (surface mail) All regions*	*Foreign countries (airmail) Region 1*	*Region 2*	*Region 3*
Institutional†	$50.00	$65.00	$90.35	$114.35	$138.35
Individual‡	$31.00	$46.00	$71.35	$95.35	$119.35
Student resident‡	$24.80	$39.80	$65.15	$89.15	$113.15

Single copies are $4.50 Remittances should be made by check draft post office or express money order in U S funds drawn through a U S bank, payable to this Journal.

Airmail breakdown—*Domestic* First-class and Priority rates for the U.S and possessions are available upon request *Region 1* Central America islands, and mainland colonies of European countries in The Americas. *Region 2* South America Europe Egypt Africa (bordering the Mediterranean) *Region 3* Asia, Australia Africa (other than Mediterranean) Middle East, Far East, The Pacific, U.S.S.R. (and constituent Republics)

†Institutional (multiple reader) subscriptions are available to public and private libraries schools, hospitals and clinics city county state provincial and national government bureaus and departments and all commercial and private institutions and organizations.

‡Individual subscriptions and all student rate subscriptions must be in the names of billed to and paid by individuals. All student rate requests must indicate training status and name of institution

Subscriptions may begin at any time

Second class postage paid at St. Louis Mo and additional mailing offices

Printed in the U.S.A. copyright © 1980 by The C V Mosby Company

for "cardiac separation"...

Although over 80% of post coronary patients can resume normal marital sexual activity fear of anginal pain often results in "cardiac separation" between patients and their families

You can help minimize "cardiac separation" with a program of counseling and often with a prescription for Cardilate (erythrityl tetranitrate)

Cardilate increases exercise tolerance helps patients return to more normal levels of activity—including sexual activity

Sublingually Cardilate begins to work within 5 minutes eliminating or reducing frequency and severity of anginal pain for up to 2 hours

counsel & Cardilate

(erythrityl tetranitra

CARDILATE

INDICATIONS ... for the prophylaxis and long-term treatment of patients with frequent or recurrent anginal pain ...

CONTRAINDICATIONS

WARNING Data supporting the use ...

PRECAUTIONS

ADVERSE REACTIONS

... Alcohol may enhance this ...

DOSAGE AND ADMINISTRATION

HOW SUPPLIED

CARDILATE ... TABLETS ... Bottle of 100 ...

Burroughs Wellcome Co
Research Triangle Park North Carolina 27709



Contents *continued*

continued on page 9

which is why Burdick offers a choice.

Like any other professional instrumentation an exercise tolerance system can be right for one physician and something less (or more) for another The right choice depends on your practice preferred protocols staff budget an i other considerations

That s why Burdick offers a choice of ExTOL™ systems to match you neeas thout resorting to a combination of componen at lack the instru ment compatability and one ource serviceability of a Burdick ExTOL system

We offer three ba r ise tolerance systems with a wide choice of options — single or three-channel cardiographs single or multi channel monitors defibrillators and our economical TMS-400 or deluxe TMS 300 treadmill with remote control and programmer In short we have an ExTOL system that s right for your practice your particular needs

For complete information about ExTOL or a demonstration call or write
The Burdick Corporation, Milton, Wis 53563



Toll free 800-356 0701
In Wisconsin 608 868 7631

BURDICK

Contents *continued*

continued on page 11

VARIAN V-3400

Setting New Standards In Sector Scanning

FEATURES

Digital Scan Processor (DSP)

The Varian DSP uses a powerful microprocessor system to fully utilize digital technology for processing the ultrasound image

Phased Array Design

Varian pioneered the success of phased array transducer technology which requires no moving parts and yields significant performance advantages

Varian Ultrasound

From pioneer to premier manufacturer Varian is a major high-technology corporation consistently leading the way in product technology, responsive field service and customer education

BENEFITS

Excellent Imaging Quality

The V 3400 produces clear low noise high sensitivity, diagnostic quality images from all major anatomic windows

Dependable Performance

Inherent reliability solid state electronics and phased array design combine with Varian s experience and extensive customer support to ass dependable clinical performance

Advanced Clinical Capability

Fast accurate examinations recording and quantitation are enhanced by the V-3400 advanced clinical features such as variable persistence pre and post processing simultaneous M mode and the light pen measurement system



To learn more contact Medical Group Varian Associates Inc 611 Hansen Way Palo Alto CA 94303 Tel 415/493-4000

Contents *continued*

(Information for authors on page 19)

(Index to advertisers on page 40)

The appearance of a code at th bottom of the first page of an riginal article in this journ l indicates the copyright own r s consent that c p es of the article m y be made for personal or internal use or for th personal o internal use of specific cl nts This consent is given on the condition, howeve that the copier pay the stated per copy fee through th Copyright Clearance C nter Inc 21 Congress St Salem, Mass 01970 617 744-3350 for copying beyo d that permitted by Sect ons 107 or 108 of the U S Copyright Law This consent does not extend to other kinds of copying such as copying f r general distribution for advertising o promotional purposes, for cr ting new collective works or for resale



One disposable dome stands out from every other in sight Why? Probably because Bell & Howell s DISPOSADOME® excells in so many ways

Some say they like the convenience It s so fast and easy! (They refer to the individual snap open sterile package and quick installation — you don t have to use a fluid between the membrane and the transducer diaphragm — and of course the disposable feature)

Some quote the economy factor (Yes, considering the time and labor costs for cleaning and sterilizing other types — plus the possibility of transducer damage — that s certainly true)

Others agree to these advantages but additionally cite the ready availability of either Linden or Luer fittings (And we might add you can switch transducers or domes without disturbing the fluid path)

Whatever your reasons for helping to make DISPOSADOME famous you also have the assurance of the Bell & Howell name and experience And that s really the best reason of all

(DISPOSADOME is designed exclusively for use with Bell & Howell physiological pressure transducers.)

360 Sierra Madre Villa Pasadena California 91109 (213) 796-9381

BELL & HOWELL

American Heart Journal

Copyright © 1980 by The C. V. Mosby Company

Contents

continued on page 7

Vol. 100, No. 6, part 1, December 1980. The American Heart Journal is published monthly by The C. V. Mosby Company, 11830 Westline Industrial Drive, St. Louis, Mo. 63141. POSTMASTER: Send address change to above address.

1981 Annual subscription rates	U.S.A.	Foreign countries (surface mail) All regions	Region 1	Foreign countries (airmail) Region	Region 3
Institutional†	$50.00	$6[illegible].00	$90.[illegible]	$114.35	$1[illegible]3[illegible]
Individual‡	$31.00	$46.00	$[illegible]1.35	$9[illegible].35	$119.35
Student, resident‡	$[illegible]4.80	$39.80	$65.15	$89.15	$113.15

Single copies are $4.50. Remittances should be made by check, draft, post office or express money order in U.S. funds drawn through a U.S. bank, payable to this Journal.

Airmail breakdown—*Domestic:* First class and Priority rates for the U.S. and possessions are available upon request. *Region 1:* Central America, islands, and mainland colonies of European countries in The Americas. *Region 2:* South America, Europe, Egypt, Africa (bordering the Mediterranean). *Region 3:* Asia, Australia, Africa (other than Mediterranean), Middle East, Far East, The Pacific, U.S.S.R. (and constituent Republics).

†Institutional (multiple reader) subscriptions are available to public and private libraries, schools, hospitals, and clinics, city, county, state, provincial and national government bureaus and departments, and all commercial and private institutions and organizations.

‡Individual subscriptions and all student rate subscriptions must be in the names of, billed to, and paid by individuals. All student rate requests must indicate training status and name of institution. Subscriptions may begin at any time.

Second class postage paid at St. Louis, Mo., and additional mailing offices.

Printed in the U.S.A. copyright © 1980 by The C. V. Mosby Company

Remember

ZYLOPRIM°

the original (allopurinol)

100 and 300 mg

Scored Tablets

The name
Zyloprim
is now
imprinted on
each tablet







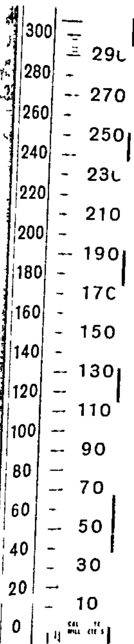
Burroughs Wellcome Co
Research Triangle Park
North Carolina 27709

Contents *continued*

continued on page 9



continued on page 11


300
280
260
240
220
200
180
160
140
120
100
80
60
40
20
0
290
270
250
230
210
190
170
150
130
110
90
70
50
30
10

Letters to the Editor

continued on page 13

A living presence

ARDIOLINE thirty years of xperience in the field of recording 'ectromedical phenomenon and f collaboration with the medical rofession.
ARDIOLINE technology and now-how resulting from daily narketing and the diligent evelopment of cardiological ipment throughout the world DIOLINE in hospitals 'iagnostic centres outpatient clinics nd private medical studios living presence

CARDIOLINE equipments are made accordance with the most ngest international Safety andards (I.E.C. 601/1 ☰♥)

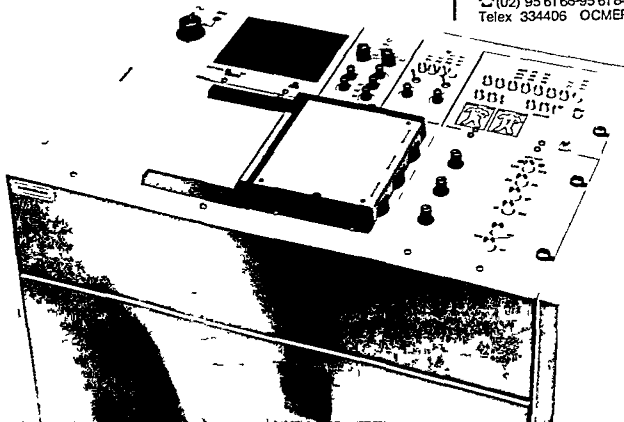
In addition, they are based on a "completely modular concept they can be run both on mains supply or on battery and are therefore completely reliable in all places under all conditions
In short, eta-system stands for accurate and essential design made in functional and practical materials
Thanks to these guarantees" the Cardioline eta-system appliances *have become a constant aid in the* support and at the service of the medical profession.

3-channel poligraph trolley housing composed by
- 3-channel ECG recorder and lead selector



- phono set
- *pulse set*
- 3 channel monitor

REMCO ITALIA SPA
20060 S Pedrino di Vignate
Milano Italy
☎(02) 95 61 68-95 61 84 95 604
Telex 334406 OCMER I



Contents *continued*

(Information for authors on page 19)

(Index to advertisers on page 32)

The appearance of a code at the bottom of the first page of an original art l in this journal indicates the copyright owner ns nt that cop es of the articl may be made for personal o internal use or for the personal or internal use of specific clients This c nsent is gi en on the condition howe er that the copier pay the tated per copy fee through the Copyright Cl rance Center Inc 1 Congress St., Salem Mass 01970 617 44-3350 fo copying beyond that permitted by Sections 107 or 108 of th U S Copyright Law This consent does not extend to oth r kinds of copying such as copying for general distribution for advertising r promotional purposes for creating new collecti e works or for resal

American Heart Journal
December 1980 Volume 100 Number 6 part 2

PROCEEDINGS OF THE

Symposium on cardiac arrhythmias

A DECADE OF PROGRESS—1980

MAY 8 10 1980
Stanford University Medical Center
Palo Alto California

Guest Editor Donald C Harrison M D

Sponsored by an educational grant from
ASTRA PHARMACEUTICAL PRODUCTS INC
Framingham, Massachusetts

American Heart Journal

Copyright © 1980 by The C V Mosby Company

Contents

continued on page 4

Vol 100 No 6, part 2, December 1980 The Ameri an He rt Journal is published monthly by The C V Mosby Company 11830 Westli e Industrial Dri e St. Louis, Mo 63141 POSTMASTER Send address hange to abo e address.

1981 Annu l subscript on rates	U.S.A	Fore gn countries (urface ma l) All region.	Foreign countries (a rma l) R gion 1	R gion 2	Region 3
Institutional†	$50 00	$65 00	$90.35	$114 3	$138 35
Individu l‡	$31 00	$46 00	$ 1.35	$ 95.35	$119.35
Student resident‡	$ 4.80	$39 80	$65 15	$ 89 15	$113 15

Single copies re $4.50 Remittan es sh uld be made by heck draft, post office or p ess money order in U S funds drawn through a U S bank pay bl to this Journal.

Airmail breakdown—*Domestic* First-class and Pri rity rates for the U.S and possession re available upon request *Region 1* Central America isl nds, and mainl nd colonies of Eu opean countries in The Americas *Region 2* South Am rica, Furope Egypt Africa (bord ri g the Med terra ean) *Region 3* Asia Australia Africa (oth than Med terrane n) Mid ll East, Far East Th Pacifi U S.S R (and constituent Republics)

†Inst tuti nal *(multiple read) subscripti ns* are availabl to publ and pri ate libra es, schools hospitals, and clin cs c ty cou ty state provin ial and n tion l government bureaus and departments and all comme cial and pri te institut ons and organ zations.

‡Individual subscriptions and all student t subscript ons must be in th n mes of b lled to and paid by individuals. All tudent r t requests must indicate training *status and name of* institut n. Subscriptions m y begin t any time

Second class postage paid at St. Louis Mo and additi n l mailing offices.

Printed in the U.S.A. copyright © 1980 by The C V Mosby Company

V Other antiarrhythmic studies

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients This consent is given on the condition however that the copier pay the stated per copy fee through the Copyright Clearance Center Inc., 21 Congress St Salem, Mass. 01970 617 744 3350 for copying beyond that permitted by Sections 107 or 108 of the U S Copyright Law This consent does not extend to other kinds of copying such as copying for general distribution for advertising or promotional purposes, for creating new collective works or for resale

American Heart Journal

July 1980 Volume 100 Number 1

Editorial

Thomas Young, M D (1773-1829)

The mechanical motions which take place in an animal body are regulated by the same general laws as the motions of inanimate bodies
Thomas Young 1808

J D Laird
Leiden The Netherlands

Thomas Young physician natural philosopher and philologist possessed beyond doubt one of the truly greatest minds at work as the eighteenth century drew to a close His contributions to our understanding of both ourselves and the world around us were legion and although this by itself would be reason enough for a few moments reflection and indeed homage in 1980 I feel compelled to seek further rationalization for intruding on the busy schedule of the cardiovascular specialist

A Frenchman is said to have remarked when considering the contribution of William Harvey that the facts were all there and indeed were so simple that any schoolboy would have been able to put them together It was nonetheless Harvey who did so And where is that clever schoolboy at this point of time in the evolution of our understanding of cardiovascular disease and particularly of ischemic heart disease? This multifactorial disease seems to present an intellectual challenge *just* beyond the grasp of the established investigators of today Was it really so much *easier in the good old days when the body of* knowledge was so much smaller that one person could develop a commanding knowledge over a broad area of science? I doubt it

We are not the first generation forced to grapple with concepts beyond both our reach and understanding so perhaps we can profit from considering the accomplishments and indeed the failures of one of the most adroit interdisciplinary intellects of all time Books have been written (see bibliography) about Thomas Young's many and varied accomplishments and in the short space of this article I wish to call attention to some of his lesser contributions of particular interest to the cardiovascular specialist For it is the curious burden to be borne by the greats that these lesser contributions often fail to receive the attention they deserve Achievements which for a lesser mortal might constitute success beyond imagination are doomed to be forgotten so overshadowed are they by other pinnacles of intellectual brilliance And so it was with the lesser contributions of Thomas Young As great as they were they paled when seen in the light of his brilliant discovery of the principle of wave interference of light his unravelling of some of the mysteries of physiological optics or his discovery of the clue to the decipherment of the Rosetta Stone eventually leading the western world to the key for unlocking the cultural treasures of ancient Egypt

Was it his genetic material or the environment of his youth which fell a goodly number of standard deviations away from the mean of his

From the Department of Physiology and Physiological Physics, Faculty of Medicine Leiden University Leiden The Netherlands

Received for publication May 30 19 9

Reprint requests to J D Laird D Phil Professor Physiological Physics, Dept of Physiology and Physiological Physics Faculty of Medicine Leiden University Wassenaarseweg 6 Leiden The Netherland

000?-8703/80/0/0001 + 08$00 80/0 © 1980 The C V Mosby Co



Fig 1 Thomas Young M D F R S From an engraving by Henry Adlard based on the portrait by Sir Thomas Lawrence (181) showing Dr Young at age 44 (Photo with the kind permission of the Science Museum London)

fellow men? Probably both but in what measure each contributed to his genius is unknown and every proposition is pure conjecture

The 1 th of June 1773 does not catch England at its best As personal intolerance was on the wane at home turbulence and conflagration become more and more characteristic of foreign affairs In the western counties of England little of this could be felt and such was the isolation that the little village of Milverton eight miles from [illegible] counties of Somerset knew little more of the world than the decline of the wool industry [illegible] the backbone of the local agri[illegible] Young s father Thomas Young [illegible] a successful mercer and [illegible] diversified into banking As [illegible] of Milverton so enervated [illegible] tual and cultural life of Thom[illegible] more important than the con[illegible] tability of his parents were their [illegible] tions They were members of the Society of Friends or Quakers Although tolerance was on the rise again this was not an easy thing to be in the England of 1773 The scars both literal and cultural on the family circle plus the dogma of this faith itself fostered an intense adherence to the serious strictures of the sect as well as stimulating a nearly obsessive self reliance and personal responsibility The Quakers belief in an inner light and the obligation of each individual to continually search in and through himself for the truth formed a driving force in Thomas Young s early education which is difficult to imagine today

A compilation of his early education is enough to cause the present day student of medicine or physics including this author to stop be silent and reflect for a few moments Upon reaching the age of two he had learned to read with in his own words considerable fluency and before reaching the grand age of four had read the bible twice through For unclear reasons he spent the better part of his first seven years with his maternal grandfather Robert Davis in Minehead One reason may simply have been practical he was the eldest of ten children or it may have been the early recognition that this genius required special care In any event he soon became a favorite of Mr Davis Young Thomas apparently took to heart the oft repeated admonishment of his grandfather that A little learning is a dangerous thing Drink deep or taste not the Pierian spring After an abortive year and a half at a miserable boarding school he spent six months of his eighth year at home In these months he spent a good deal of time at the home of his neighbour a Mr Kingdon a practical man of great ingenuity who had raised himself from tailor to land surveyor This encounter is significant for its demonstration of an early interest in science There he found many books relating to science and particularly a Dictionary of Arts and Sciences in three volumes folio which I began to read with the most intense interest and delight at this house I also found several mathematical and philosophical instruments The following spring when nearly nine years old he was sent off to a boarding school in Compton Dorset The Compton school s contribution to the nurturing of the phaenomenon Young appears to consist of equal parts classical education with emphasis on Greek Latin French Italian and Hebrew and the informal education provided by Mr Josiah

Jeffrey the school s usher and apparently also its entrepreneur It seems he had a lively private trade going with the young scholars in paper copper plates copy books and colours Jeffrey lent Young *Martin s Lectures on Natural Philosophy* the optical part of which especially caught the boy s fancy The pre teen Young under the tutelage of Jeffrey further broadened his skills by learning the use of a lathe the making of a telescope grinding and preparation of colours and the binding of books Already he apparently demonstrated a nearly obsessive and jealous guarding of his precious time which as his biographer Wood demonstrates he quite literally carried to his deathbed In his own words I was in the habit of rising an hour sooner than my school fellows in summer and of going to bed an hour or two later in winter for the purpose of mastering my lession for the day my school business was thus soon finished

None of the writings concerning Thomas Young give any really clear indication of the process by which his career choice was made Apparently it was just as random a process as with more mortal souls As fate would have it his uncle was the very successful rich and influential physician Richard Brockelsby (1722 1797) Before leaving school at the age of 13 Thomas had a brief encounter with Morris Birkbeck from which he imbibed a wish to study Botany This wish apparently took a turn later towards Medicine though not before he acquired a lathe of his own and had made himself a microscope Via a complex net of family and Quaker friends arrangements were made for his further education At 14 he was sent off to Youngsbury to become the study companion of Hudson Gurney (1777 1864) who later became a rather well known antiquary writer and member of parliament Both boys labored under their tutor a well respected and some say brilliant John Hodgkin However there seems to be in the case of Young some uncertainty with respect to who was doing the tutoring Method notwithstanding Young s knowledge of languages flourished in this period and a copybook containing extracts of the Bible in English French Italian Greek Hebrew Chaldee Syriac Samaritan Arabic Persian Turkish and Aethiopic are admired by his biographer Peacock for of all things their beautiful penmanship

This period of intense scholarship and accomplishment was suddenly interrupted at the age of 16 by a serious respiratory illness verging on consumption With careful nursing he eventually recovered though it was apparently serious enough to elicit a letter from his physician uncle Richard Brockelsby admonishing him to take better care of himself and expressing the opinion that eating a little fish twice or thrice a week would do no harm but you must make the trial cautiously In the same letter his uncle takes Thomas to task for his prudery about abstaining from the use of sugar on account of the Negro Trade In those times this was a form of symbolic protest fairly common among Quakers and other activists

By the time he left Youngsbury at the age of 19 not only was his classical education up to a level which allowed him to discuss as an equal with the scholars of his time but moreover he was widely read in science having ploughed through the works of Newton Linnaeus Lavoisier and Black and Boerhaave

He spent little time at home during this period and four months each winter were spent in the London home of the Barclays in Red Lion Square This seemingly insignificant fact is nonetheless noteworthy for it gives us a hint of the process by which Young s eventual career choice was made It was a chance for Young to sample the civilized life of cultured London to attend concerts lectures to move in literary circles to polish his social graces and to try out his intellect against worthy competition Moreover it was in the periods of his London residence that his remarkable abilities came to the attention of his uncle Brockelsby who it would appear was largely responsible for steering Thomas Young in the direction of Medicine

As an interesting aside the practice of medicine was in those days still referred to as the practice of Physic whereas what we now call physics was termed Natural Philosophy the quite arbitrary and artificial distinction between the two fields being hidden by changes of language Both Physics and Physician stem from the Greek φυσικοσ meaning Natural [1]

Young s approach to problems was strongly influenced by firm belief in several guiding principles As I have already mentioned he jealously guarded his life against the dangers of wasting time Hudson Gurney his study companion wrote of Young that at no period of his life

was he particularly fond of repeating experiments or even of very frequently attempting to originate new ones considering that however necessary to the advancement of science they demanded a great sacrifice of time, and that when the fact was once established that time was better employed in considering the purposes to which it might be applied or the principles which it might tend to elucidate Moreover he was personally persuaded of both the effectiveness and advantage of self study and at 19 wrote to his brother, Robert

Although I have readily fallen in with the idea of assisting you in your learning yet it is in reality very little that a person who is seriously and industriously disposed to improve may not obtain from books with more advantage than from a living instructor Something is wanting for the direction of application in the right path but it must be the strength of the traveller and not of the guide that must conquer the difficulties of the journey Masters and mistresses are very necessary to compensate for want of inclination and exertion but whoever would arrive at excellence must be self taught

As Peacock asks What then were the primary causes of the extraordinary success of an education conducted for so many years with so little communication with other minds with so little assistance from extrinsic sources? The principal of these must be referred to the peculiar constitution of his own mind to his great industry, to the conviction which he always felt that what one man had accomplished another might accomplish also

Young himself in a letter to his uncle in 1792 quotes some lines of a poem by Barnard as expressing his view Thou say st not only skill is gained But genius too may be obtained by studious imitation Peacock continues He had little faith in any peculiar gifts of genius believing the original difference between human intellects to be much less considerable than it was generally supposed to be His temper also in early youth was singularly unruffled and tranquil he had no boyish tastes or amusements he was educed by no dreams of the imagination from the assiduous cultivation of understanding This briefly was the young man of 19 who set off to London to study medicine in 1792

Young followed lectures in the Hunterian School of Anatomy founded by William Hunter and set forth by Bailie and Cruikshank It is difficult to visualize today but in those days the ' West End was still very nearly just that and the anatomy lectures were held in a small building on Great Windmill Street which has long since been incorporated into the Lyric Theatre on Shaftsbury Avenue It would appear that the interest in Anatomy in the Soho district of London has deeper cultural roots than might at first be evident

Young was very quick to distinguish himself demonstrating his almost uncanny ability to reach into his already vast store of knowledge (in this case, optics) and apply it to his current area of study While dissecting the eye of a recently slaughtered ox he became intrigued by the mechanism of accommodation His investigations led him to the conclusion among other things that variation of the focal length of the lens itself was responsible Young communicated his finding in a paper read to the Royal Society in May 1793 This paper by a second year student caused something of a stir embroiling him in a not altogether pleasant debate concerning both the correctness and the originality of his work While others debated the latter Young himself questioned the former Both were eventually resolved and in the summer of 1794 Young was elected to Fellowship of the Royal Society on the strength of this work

Having begun with something of a splash Young on whose advice is not clear journeyed on horseback to Edinburgh to continue his studies Armed with letters of introduction and a curiosity as broad as his knowledge he made quite a tour of it In his travels through Derbyshire and Yorkshire he examined with his accustomed activity and intelligence the collections of art or natural history mines mineral springs manufactures or other curiosities Having spent some time visiting Erasmus Darwin the grandfather of the great naturalist he left with yet another letter of introduction to an Edinburgh friend stating He unites the scholar with the philosopher and the cultivation of modern arts with the simplicity of ancient manners

The medical school of Edinburgh then so highly regarded by most did not escape without the criticism of its new student While he later concludes that Edinburgh had much to recommend it to the student of medicine he was able to share his attention between his study and taking flute lessons learning to dance to enjoy the

theater and other naughty things he had missed in his strict upbringing I hasten to add that the list of activities makes very light reading by current standards

Having taught himself German he set off to continue his studies in Gottingen and so it was that on the 10th October he left Yarmouth on the packet boat Although the university enjoyed a very high reputation at that time Young was not sad to leave with his doctorate in July 1796 He had already become accustomed to being treated as an equal by the respected top and found the formality of German university life not his cup of tea

It would seem that professional bureaucracy is not a new invention for on his return to England Young ready to practice medicine was tripped up by the fine print of regulations Although a bit oversimplified the practical consequence of the rules was that in order to become a fellow of the College of Physicians a degree from either Oxford or Cambridge was required Thus rather reluctantly and largely as an expedient he entered Emanuel College Cambridge and shall barely keep the term for two years which will be more convenient to me than

His lack of commitment to his formal study in Cambridge did give him the spare time for an active social life as well as the opportunity to do some experimental work on the propagation and character of both sound and light waves These ideas first occurred to Young while he was working on his dissertation in Gottingen and were written up in the summer of 1799 after his completion of the required six terms of residence in Cambridge Thus in the last year of the 18th century Thomas Young set off on his dual career as physicist and physician

It is hard to believe that just one man was responsible for his output during that first decade of the 19th century

In 1801 he was appointed Professor of Natural Philosophy at the recently founded Royal Institution and began at once preparing a Course of Lectures on Natural Philosophy and the Mechanical Arts Young set as his goal a complete review of the state of knowledge in Physics up to that point and attempted to cast it all in language suitable for a mixed audience

The enormous diversity of his mind is nowhere more evident than in these lectures It is easy to presume that in those days the body of knowledge was so circumscribed that all that was known could be comprehended by one albeit clever man Those were the days when a physician could do fundamental and significant research in physics—the days before the information explosion before the Xerox machine It was therefore something of a shock to note Thomas Young s words in the Preface to the published lecture notes which appeared in 1807 I had in some measure pledged myself to make a catalogue of the best works already published on the several subjects with reference to such passages as appeared to be most important Hence arose a catalogue of references respecting which it is sufficient to say that the labour of arranging about twenty thousand articles in a systematic form was by no means less considerable than that of collecting them The transactions of scientific societies and the best and latest periodical publications which have so much multiplied the number of the sources of information constituted no small part of the collection which was thus to be reduced into one body of science

Notwithstanding the comprehensive nature of the lectures or the original ideas they contained the series of 31 lectures the first year expanded to 60 the second was not a great success It appears that in striving to achieve a balance between rigor and completeness on the one hand and comprehension by a mixed audience on the other he badly misjudged the general public This is in contrast to the far more successful but less original lectures of Davy on chemistry given at about the same time

Young s lectures have achieved a form of immortality granted only a very few It is in the thirteenth lecture that he introduces the concept of a modulus of elasticity with which his name is still associated It must be conceded that even a well taught mechanical engineer would have difficulty reçognizing Young s Modulus of Elasticity as defined in that lecture The modulus of elasticity of any substance is a column of the same substance capable of producing a pressure on its base which is to the weight causing a certain degree of compression as the length of the substance to the diminution of its length In fairness to Young it must be realized that he was wrestling with the concepts of what we now call stress and strain without the benefit of the contributions of calculus or the great French mathematician Cauchy who sorted it all out in his 1822

paper for the French Academy of Sciences The definition of Young s modulus in terms of the slope of the stress strain curve was actually proposed by Navier in 1826

In the same lecture Young applies the concept of a stress without naming it to muscle mechanics noting that it is obvious that in muscles of the same kind the strength must be as the number of fibres or as the extent of the surface which *would be formed by cutting the muscle* across

In 1802 Young delivered the Bakerian Lecture to the Royal Society On the Theory of Light and Colours in which he put foreward what is in slightly modified form known today as the Young Helmholtz theory of color vision

Perhaps his most important contribution was to the theory of light itself which he developed in a series of four papers published during the first four years of the 19th century Although only 30 at the time these papers represented the culmination of a train of thinking reaching back into his youth As a boy he was fascinated by optics His researches for his dissertation in Gottengen were devoted to an attempt to derive a system or alphabet for describing all the sounds which could be formed by the human voice thus forming a basis for an alphabet for all languages Via his studies on the formation and propagation of sound he began to see analogies with the propagation of light Building on this base the concepts were expanded during the ample spare time available to him in his Cambridge days and were presented in his 1800 Philosophical Transactions paper entitled Outlines of Experiments and Enquiries Respecting Sound and Light Unfortunately young Thomas in this paper *needlessly* took a rather mean swipe at the eminent mathematician and astronomer Dr Smith and one may speculate that in view of later events he would have wished for more self control

His subsequent three major papers set out with uncommon clarity the basis for the wave theory of light including an unambiguous statement of the principle of superposition of waves leading to *interference patterns In a minor* but nonetheless intriguing paper published in 1802 in the Royal Institution Journal under the title Harmonic Sliders *he gives details of a simple machine* for visually demonstrating the effect of superposition of sine waves coming very close to *enunciating* what we now call Fourier synthesis In 1807 with *the publication of his* Course of Lectures on Natural Philosophy Young essentially rounded off his momentous contribution to the subject

One would expect that such a profound series of papers on a subject which had been festering unresolved since Newton s efforts would have shaken the world of science causing great excitement Nothing could be further from the truth Young was quite simply ignored and the vast majority of active scientists apparently failed to grasp the significance of his work Even more painful was the vehement attack on his work and his imprudent remarks on Smith by Robinson and subsequently by Brougham The exchanges were increasingly nasty and founded more on personal dislike than on scientific merit They achieved their end to inflict pain and to cast doubt upon Young s reputation as a physicist Even more *difficult* for him to accept was the prejudicial effect on his medical practice which already was suffering from a certain dilution of attention In gross oversimplification it was a dark period for Young personally and for the development of the theory of light up until Fresnel s original and powerful support given in 1815 1816 As Wood states in his extensive account of Young s contributions Fresnel must *be reckoned as sharing with Young the honour of* establishing the wave theory on a broad and sound basis In Young s own words The theory of light and colours though it did not occupy a large portion of my time I conceived to be of more importance than all that I have ever done or ever shall do besides

And what did Thomas Young do with all his spare time during the development of his ideas *on light*? Among other things he made a contribution which is to this day of significance to the practicing cardiologist The law of LaPlace as we know it today relates the pressure difference across a curved surface to the tensions which must obtain at the surface itself *It constitutes an* extremely powerful concept for relating the forces which must be developed by the myocardium to raise the required pressures in the ventricle Not only is hypertension an excessive load on heart muscle but less obvious and equally true a big heart is a bad heart Now it so happened that LaPlace read his paper on the subject in 1805 and published it in 1806 But on the 24th of December 1804 Young presented his Essay on the Cohesion of Fluids to be published in the *Philosophi*

cal Transactions of 1805 The rival claims of priority by these two giants took some time to be resolved and although there was controversy it was pale by comparison with the debate over the theory of light In a feeble attempt to redress the matter I personally now refer to the relationship as the Young LaPlace Law The supplement to the fourth edition of the Enclycopaedia Brittanica contains a more fully developed article by Young in which he not only presents the Young LaPlace Law but also makes the very first estimate of the diameter of a molecule getting within a factor of 100 correct which was pretty good going for the beginning of the 19th century

Another contribution which may interest the cardiologist was his invention of the kymograph which in the hands of physiologists has revealed most of what we know of the processes of life A drawing of an elementary form of this device is contained in the plates accompanying the published version of his lectures on natural philosophy

In the *Philosophical Transactions of 1809* he published the text of his Croonian Lecture before the Royal Society On the Function of the Heart and Arteries This together with his paper entitled Hydraulic investigations subservenient to an intended Croonian Lecture on the motion of blood which appeared in the year before constitute a milestone in cardiovascular mechanics In the 1808 paper Young gives an analysis of the pressure flow relations in tubes and was well ahead of his time in describing the scaling laws of such a flow The relative importance of the square law vs the linear Poiseuille like term are discussed as a function of dimensions velocity viscosity etc In fact the essence of scaling with Reynolds number is clearly enunciated roughly 40 years before Osborne Reynolds carried out his crucial experiments

In the same papers Young analyzes for the first time the nature of pulsating flow in distensible vessels He derives an expression for the speed of propagation of waves in arteries and gives the method for computing it although once again without calculus and the modern definition of Young s modulus this formula is couched in rather obscure and impenetrable language The modern form of this expression is generally referred to as the Moens Korteweg equation and was presented roughly 70 years later In a clear and straightforward line of reasoning Young applies these concepts to deductions concerning the nature of the pulse in various pathological states and with a view to resolving the debate over whether the muscular coat of arteries play a role of significance in blood flow He concludes against the operation of the muscular powers of the arteries in the ordinary circulation

In 1803 after two years of lecturing on natural philosophy embroiled in controversy and concerned with the progress of his medical practice he resigned his professorship at the Royal Institution in the hope of devoting a greater part of his attention to medicine

In 1811 Young joined the staff of St Georges Hospital and remained happily associated with the hospital until his death 18 years later He set out to do for the practice of Physic what he already had done for physics to set down in a form nearly similar relating to every department of medical knowledge it will be comparatively more concise than these lectures [on natural philosophy] in proportion to what has been said and written respecting physic but I hope much more complete with regard to all that is known with certainty and can be applied with utility The results of these labors was *An introduction to Medical Literature including a system of Practical Nosology intended as a guide to students and an assistant to practitioners* published in 1813

In this work the first chapter contains some interesting glimpses of his views on the practice of medicine and on the most appropriate education illustrating his lack of comprehension of the limitations of his less well endowed fellowmen I shudder to think what would be the reaction of our students today were we to put into practice his belief that his own lectures on natural philosophy probably contain as much of natural philosophy as is absolutely *necessary for* a medical student Once again he was not a popular lecturer badly overestimating his audience

As near as can be determined it would seem that Young was a competent physician but never succeeded in attaining any real measure of popularity or success Peacock blames this on Young s approach to patients gentle and gentlemanly but not genial Both Wood and Hervel support the view of Young s colleague Dr Brodie who attributes his lack of success to the lack of constant attention to nurturing his practice due

to the demands of his other interests His practice slowly declined as his interests turned to Egyptology to which he made major contributions and because of his tasks of Secretary of the Board of Longitude and Superintendent of the *Nautical Almanac*

Sadly very little seems to be known of his private life In the summer of 1804 he was married to Eliza Maxwell and this relationship would appear to have been quite simply a happy and affectionate one In 1821 they travelled together to the continent and in the course of this rather grand tour he met with LaPlace In 1827 Thomas Young was elected as Foreign Member of the Academy of Science at Paris succeeding to the chair left by the death of Volta earlier that year

Early in 1829 Young began to suffer from repeated attacks of asthma and general weakness He managed to muster the strength to continue attendance at the Council meetings of the Royal Society his last being the 26th of March 1829 In bed he struggled with pencil for he could no longer hold a pen fast to complete his *Rudiments of an Egyptian Dictionary*

Thomas Young died on the 10th of May 1829 at the age of 56

In the seventh volume of the case notes of Dr Brodie one finds a page Examination of the Body of the late Thomas Young M D For Sec Royal Soc May 11, 1829 The cavities of the heart but especially those of the left ventricle were of unusual thickness (The latter might be of double the usual thickness) The sigmoid valves of the aorta were very slightly ossified in spots The aorta from its origin to its bifurcation was ossified to a very great extent so as to form thoughout the greater part of its extent a hard unyielding tube No man alive then and only a few after him would have understood as well as Thomas Young the significance of these findings

Throughout his life there is a sad strain of unfulfillment and frustration so undeserved since we are all so much richer for his contributions In 1813 Young wrote I think if I happen to live to be about 200 I shall begin to reap some little credit and emolument from the labours of my youth—but at 100 I shall be still a boy in public opinion

I would like to express my appreciation to the staff of the Libraries of the Royal Society Museum for the History of Science and Technology Science Museum and the Wellcome Institute for the History of Medicine all in London for their assistance Moreover most of the quotations are extracted from the biography of Young by G Peacock or from that by A Wood Those who may wish to pursue Thomas Young s contribution to their special area are encouraged to consult Wood first as his book is both relatively easy to find and is a gold mine of information collected over years and years of painstaking research

Lastly I note with pleasure the contribution to my own education by Dr R T Jones also a self educated genius who among other things first introduced me to the contributions of Thomas Young

Furthermore I hope and trust that the reader will appreciate my problem in attempting to cover the contributions of so diverse a man as Thomas Young in so brief a space A selection was required and that necessarily is a very personal matter

REFERENCES

1 Peacock G Life of Thomas Young M D F R S etc London 18[illegible] John Murray
2 Peacock G and Leitch J The miscellaneous works of Dr Thomas Young 3 Vols London 18[illegible] John Murray
3 Young T A Course of Lectures on Natural Philosophy and the Mechanical Arts 2 Vols 2nd ed London 1845 Taylor and Walton
4 Young T An Introduction to Medical Literature including a System of Practical Nosology London 1813 Underwood and Blacks
5 Herivel J Thomas Young (1773 1829) Endeavour 32 1[illegible] 1973
6 Wood A Thomas Young Natural Philosopher 1773 1829 Completed by F Oldham Cambridge 1954 Cambridge University Press

Clinical communications

Heart rate levels and ventricular ectopic activity during cardiac rehabilitation

Maarten Simoons M D
Cees Lap M D
Jan Pool M D
With the technical assistance of Anja Roodenburg and Cecile van Gent
Rotterdam The Netherland

In many centers exercise programs have been developed for rehabilitation of patients after a myocardial infarction It has been recommended that candidates for participation should be screened in order to evaluate their motivation to eliminate undue risk and to evaluate the possible benefits of the program In particular several authors state that patients with frequent multiform or repetitive premature ventricular complexes (PVCs) should not be accepted for physical training unless the arrhythmia has been treated However in spite of the widespread experience with rehabilitation of cardiac patients little information is available on the actual incidence of arrhythmias during rehabilitation programs In one study heart rates and arrhythmias have been described during exercise tests and ambulatory monitoring including cardiac exercise classes However no separation was made between data during the exercise period and during other activities The present study was designed to address the following questions

1 Which heart rate levels are reached during rehabilitation of groups of patients with coronary artery disease?

2 How are these heart rates related to those during a symptom limited exercise test and during normal daily activities?

3 Which patterns of ventricular ectopic activity occur during the rehabilitation program?

4 Can these arrhythmias be predicted from either the exercise test or ambulatory monitoring during normal daily life?

Patient selection

Data were analyzed from 40 patients with coronary artery disease there were 39 males and one female between 32 and 65 years old Three other patients had to be excluded due to failure of the ambulatory ECG tape recording Thirty six patients were enrolled in the rehabilitation program after a myocardial infarction The interval between the infarction and the study was 3 to 6 months in six patients 7 to 12 months in 11 patients and 1 to 3 years in the remaining 19 patients Three patients were studied between 3 and 6 months after coronary bypass surgery Finally one patient was admitted to the program because of moderate angina pectoris At the time of the study patients had participated in the rehabilitation program between 1 and 6 months In Rotterdam patients can be referred to the rehabilitation program from several major hospitals and by private physicians In general medical therapy is provided by the referring physician Therefore indications for antiarrhythmic therapy and other drugs may vary between the participants in the rehabilitation program Actually 14 patients used no medication except anticoagulants or nitroglycerin Seventeen patients were on beta blockers seven used antiarrhythmic drugs six took digoxin and five patients received seda

From the Thoraxcenter Erasmus University Rotterdam The Netherlands.

Received for publication Oct 10 1979

Accepted for publication Nov 29 1979

Reprint requests Dr Maarten Simoons Thoraxcenter Erasmus University Rotterdam P O Box 1738 Rotterdam The Netherlands

0002 8703/80/010009 + 06$00 60/0 © 1980 The C V Mosby Co

to the demands of his other interests His practice slowly declined as his interests turned to Egyptology to which he made major contributions and because of his tasks of Secretary of the Board of Longitude and Superintendent of the *Nautical Almanac*

Sadly very little seems to be known of his private life In the summer of 1804 he was married to Eliza Maxwell and this relationship would appear to have been quite simply a happy and affectionate one In 1821 they travelled together to the continent and in the course of this rather grand tour he met with LaPlace In 1827 Thomas Young was elected as Foreign Member of the Academy of Science at Paris succeeding to the chair left by the death of Volta earlier that year

Early in 1829 Young began to suffer from repeated attacks of asthma and general weakness He managed to muster the strength to continue attendance at the Council meetings of the Royal Society his last being the 26th of March 1829 In bed he struggled with pencil for he could no longer hold a pen fast to complete his *Rudiments of an Egyptian Dictionary*

Thomas Young died on the 10th of May 1829 at the age of 56

In the seventh volume of the case notes of Dr Brodie one finds a page Examination of the Body of the late Thomas Young M D For Sec Royal Soc May 11 1829 The cavities of the heart but especially those of the left ventricle were of unusual thickness (The latter might be of double the usual thickness) The sigmoid valves of the aorta were very slightly ossified in spots The aorta from its origin to its bifurcation was ossified to a very great extent so as to form throughout the greater part of its extent a hard unyielding tube No man alive then and only a few after him would have understood as well as Thomas Young the significance of these findings

Throughout his life there is a sad strain of unfulfillment and frustration so undeserved since we are all so much richer for his contributions In 1813 Young wrote I think if I happen to live to be about 200 I shall begin to reap some little credit and emolument from the labours of my youth—but at 100 I shall be still a boy in public opinion

I would like to express my appreciation to the staff of the Libraries of the Royal Society Museum for the History of Science and Technology Science Museum and the Wellcome Institute for the History of Medicine all in London for their assistance Moreover most of the quotations are extracted from the biography of Young by G Peacock or from that by A Wood Those who may wish to pursue Thomas Young's contribution to their special area are encouraged to consult Wood first as his book is both relatively easy to find and is a gold mine of information collected over years and years of painstaking research.

Lastly I note with pleasure the contribution to my own education by Dr R T Jones also a self-educated genius who among other things first introduced me to the contributions of Thomas Young

Furthermore I hope and trust that the reader will appreciate my problem in attempting to cover the contributions of so diverse a man as Thomas Young in so brief a space A selection was required and that necessarily is a very personal matter

REFERENCES

1 Peacock G Life of Thomas Young M D F R S etc *London* 1855 *John Murray*
2 Peacock G and Leitch J The miscellaneous works of Dr Thomas Young 3 Vols *London* 1855 *John Murray*
3 Young T A Course of Lectures on Natural Philosophy and the Mechanical Arts 2 Vols 2nd ed London 1845 Taylor and Walton
4 Young T An Introduction to Medical Literature including a System of Practical Nosology London 1813 Underwood and Blacks
5 Herivel J Thomas Young (1773 1829) Endeavour 32 15 1973
6 Wood A Thomas Young Natural Philosopher 1773 1829 Completed by F Oldham Cambridge 1954 Cambridge University Press

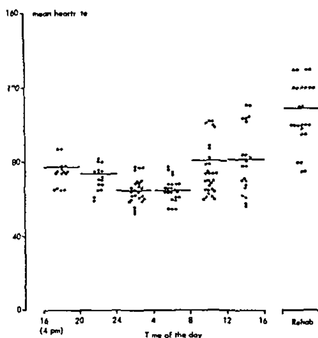


Fig 2 Distribution of the mean heart rates measured over a 24 hour period with those during rehabilitation *The horizontal line* in each column represents the mean value

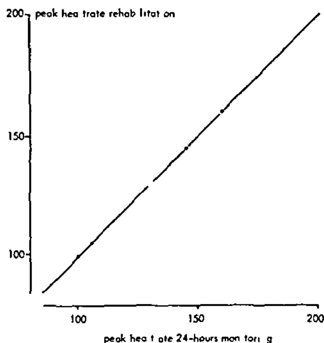


Fig 3 Comparison of the peak heart rate during rehabilitation with the highest heart rate during the preceding 24 hours.

Table III Ventricular arrhythmias during rehabilitation*

PVCs	*No of patients*
0 nil	17
1 <5/minute	14
2 ≥5/minute	1
3 multiform	2
4 repetitive	6

*Most severe type of PVC during the rehabilitation period in each individual.

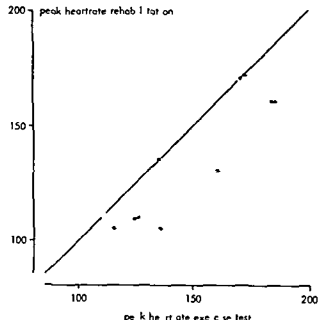


Fig 4 Comparison of the peak heart rate during rehabilitation with the highest heart rate achieved during a symptom limited graded exercise test within the same week

tion The ECGs were analyzed at high speed by trained technicians using the Medilog system (Oxford Instruments) The 24 hours preceding the training and the actual training period were analyzed separately

A symptom limited exercise test was performed within the same week Medication was not changed during this period Workload on a calibrated bicycle ergometer was increased with steps of 10 Watts per minute until near exhaustion moderate angina pectoris or dyspnea Three ECG leads were continuously recorded on paper with paper speeds of 10 and 25 mm per second alternatingly

Premature ventricular complexes were classified as shown in Table I The part of the 24 hour recording during which each type of arrhythmia occurred was indicated semiquantitatively in five classes as shown in Table II absent occasional (less than 2 hours of ECG recording) episodic (2 to 12 hours) frequent (12 to 22 hours) and

EXERCISE TEST

REHAB	0	1	2	3	4
0	12	5			
1	2	8	2	1	1
2					1
3		2			
4	2	1			3

Fig 5 Most severe grade of PVC (see *Tables II* and *III*) in each patient during the rehabilitation program *(REHAB)* compared with the highest grade of PVC during the exercise test *The dotted lines* separate patients with severe PVCs grades 2 to 4 from those with less than five PVCs per minute or without PVCs

24 HOUR MONITORING

REHAB	0	1	2	3	4
0	6	8		2	1
1		6		5	3
2					1
3				1	1
4				1	5

Fig 6 Most severe grade of PVC (see *Fig 5*) in each patient during the rehabilitation program *(REHAB)* compared with the highest grade of PVC during 24 hours of normal daily activities

continuous (22 to 24 hours) Heart rates were measured from trend plots as shown in Fig 1 The mean heart rate was measured every hour as well as the highest heart rates reached during 24 hours and during rehabilitation

Results

In Fig 2 the heart rates during the 24 hours preceding rehabilitation are compared with the mean heart rates during rehabilitation In 37 patients the mean heart rate during rehabilitation was higher than the heart rate during any hour of the preceding day and night In addition the peak heart rates during rehabilitation exceeded those during 24 hour recording in 33 out of 40 patients as illustrated in Fig 3

With the rehabilitation session peak heart rates were found during jogging in 25 patients and during volleyball in the remaining 15 patients These data indicate that most patients exercised more vigorously during the rehabilitation program than at any moment of their normal activities However even during rehabilitation many patients did not reach the same heart rate level as during the exercise test which was performed within the same week The peak heart rates during the exercise test exceeded those during rehabilitation by 10 beats or more in 20 patients (Fig 4) while in five patients the peak heart rate during rehabilitation was 10 beats higher during rehabilitation than the heart rate during the exercise test

The performance during the exercise test averaged 92% (SD = 15%) of the predicted normal values Peak heart rates in those patients without beta blocker therapy averaged 89% (SD = 12%) of the age predicted maximum heart rate in each patient

The premature ventricular complexes observed during the symptom limited exercise test are presented in Table I PVCs occurred during all stages of the test Repetitive PVCs (code 4) were only observed during the highest workload and in the recovery period The occurrence of PVCs during 24 hours of normal daily activity are given in Table II In most patients PVCs were observed occasionally In six patients frequent PVCs were present The incidence of premature ventricular complexes during the symptom limited exercise test was similar to the results of other investigators In 22 out of 40 patients the PVCs during the stress test were of lower grade than those during 24 hours of ambulatory monitoring This again is in agreement with data published by

others[8,11] In two patients however a higher grade of PVC occurred during the exercise test Apparently these two methods disclose different information regarding the electrophysiological state of the myocardium[8]

The distribution of PVC during the rehabilitation session is shown in Table III In Figs 5 and 6 the data in each patient are compared under the three different conditions exercise test normal activities and rehabilitation program It is shown that the PVCs during rehabilitation could not be predicted from the exercise ECG The sensitivity for prediction of severe PVCs (grades 2 to 4) during rehabilitation from the exercise test is only 44% (four out of nine cases) while the specificity is 87% (27 out of 31 cases) as shown in Fig 5 On the other hand all nine patients with severe PVCs during rehabilitation were detected by ambulatory ECG recording (sensitivity 100%) at the cost of a poor specificity (20 out of 31 = 64%) as presented in Fig 6 No differences in ventricular ectopic activity were observed between the patients who took digitalis beta blockers or other antiarrhythmic drugs

Discussion

In the Rotterdam Rehabilitation Program patients are exercised in groups under medical supervision but without ECG monitoring The program consists of jogging walking calisthenics and ball games Many patients were able to perform in the program at similar levels of work as in the symptom limited exercise test on the bicycle ergometer (Fig 2) Most patients reached considerably higher heart rates during rehabilitation than during their other activities The occurrence of ventricular arrhythmias was not related to the level of physical activity as represented by the heart rate Most PVCs were observed during normal activities and fewer during the exercise test and during the rehabilitation program This may be due to the length of the ECG records since the majority of arrhythmias occurred during less than 2 out of 24 hour monitoring period (Table II) while the exercise test and the rehabilitation program had a duration of approximately 30 and 60 minutes respectively

It has been recommended that patients with frequent multiform or repetitive PVCs should not be accepted in a rehabilitation program However neither the exercise test nor ambulatory monitoring provided an accurate prediction of the type of PVC seen during the rehabilitation program five patients had multiform or repetitive PVCs during rehabilitation while no PVC or less than 5/minute occurred during stress testing (Fig 5) Thus the sensitivity of exercise tests for the prediction of higher grade PVCs during rehabilitation is low Ambulatory monitoring predicted all patients with PVCs during rehabilitation However it would be impractical to exclude patients with frequent multiform or repetitive PVCs on the 24 hour recording from a rehabilitation program since these arrhythmias occur in many post infarct patients at some time or other In fact in the present series 20 out of 40 patients should have been excluded according to such a criterion while only nine of these 20 developed grade 2 to 4 arrhythmias during the actual rehabilitation session (Fig 6) Since it appeared to be impossible to predict PVCs during rehabilitation from either the exercise ECG or the ambulatory tape recording we conclude that exclusion of patients from the rehabilitation program should not be based on the observation of higher grade PVCs per se It is likely that the risk of cardiac arrest or other cardiovascular incidents is greatest in those patients with extensive left ventricular impairment especially in those with a low physical capacity and with an inadequate heart rate or blood pressure response during exercise[1,11] Selection of patients by such criteria seems more appropriate than exclusion of all those patients who show higher grade arrhythmias during an exercise test

In the present investigation no life threatening arrhythmias occurred During our total experience of 5 years of cardiac rehabilitation in Rotterdam which involved 15 000 patient hours one patient developed ventricular fibrillation This patient was successfully resuscitated and subsequently underwent coronary bypass surgery No excess mortality was reported in a recent review by Haskell which covered 30 cardiac rehabilitation programs in the USA and Canada During more than 1 600 000 hours of supervised exercise 50 cardiac arrests were reported eight of which were fatal In addition five [illegible] fatal and [illegible] fatal myocardial infarctions [illegible] as well as four other fatal cardiovascular accidents [illegible] exclusion of seven deaths [illegible] rehabilitation programs in a small group of patients [illegible] mortality rate was 1 per [illegible] patient [illegible] which corresponds to an a[illegible]al mortal[illegible]

4 1% It should be noted however that 42 patients with cardiac arrests were successfully defibrillated This indicates that the risk of cardiac arrest during rehabilitation is considerably higher than the risk during other activities in spite of the selection criteria which were applied by the various centers Therefore promotion of exercise programs for patients with coronary artery disease should be avoided unless the experienced personnel and appropriate equipment are immediately available This risk of cardiac rehabilitation can be covered effectively by personnel who have been trained in cardiopulmonary resuscitation

Summary

The heart rate levels and the incidence and types of premature ventricular complexes (PVCs) during the rehabilitation of 40 patients with coronary artery disease were compared with those during 24 hour ambulatory monitoring and during a symptom limited exercise test Thirty six patients were studied 3 months or later after a myocardial infarction and four patients were studied after coronary bypass surgery The last patient suffered from moderate angina pectoris Peak heart rates during rehabilitation exceeded those during other activities in 34 out of 40 patients Half of the patients reached even higher heart rate levels during the exercise test Twenty three patients had PVC during rehabilitation frequent multiform or repetitive PVC occurred in nine of these During the exercise test 24 patients had PVCs while PVCs were observed on the ambulatory tape recording in 34 patients Frequent multiform and repetitive PVCs occurred in eight patients during exercise testing and in 20 patients during monitoring No relation was found between either the incidence or the type of PVC in individual patients under these three condition Thus selection of patients with a high risk for arrhythmias during rehabilitation is not feasible by either exercise testing or ambulatory tape recording

REFERENCES

1 McHenry M M Medical screening of patients with coronary artery disease Criteria for entrance into exercise conditioning programs *in* Exercise in Cardiovascular Health and Disease Amsterdam E A Wilmore J H De Maria A N et al eds New York 1977 York Medical Books p 314

2 Hellerstein H K Hirsch E Z Ader R Greenblatt N and Siegel M Principles of exercise prescription for normals and cardiac subjects *in* Exercise Testing and Exercise Training in Coronary Heart Disease Naughton J P and Hellerstein H K eds New York 1973 Academic Press Inc p 129

3 Naughton J P The effects of acute and chronic exercise in cardiac patients *Ibid* p 343

4 Merriman J E Long term activity programs for coronary patients *Ibid* p 347

5 Fletcher G F and Cantwell J D Continuous ambulatory electrocardiographic monitoring Use in cardiac exercise programs Chest 71 27 1977

6 Pyfer H R Mead W F Frederick R C and Doone B L Exercise rehabilitation in coronary heart disease Community group program Arch Phys Med Rehabil 57 335 1976

7 Simoons M L and Hugenholtz P G Gradual changes of ECG waveform during and after exercise in normal subjects Circulation 52 570 1975

8 Ryan M Lown B and Horn H Comparison of ventricular ectopic activity during 24 hours monitoring and exercise testing in patients with coronary heart disease *N Engl J Med 292 224 1975*

9 Goldschlager N Cake D and Cohn K Exercise induced ventricular arrhythmias in patients with coronary artery disease Am J Cardiol 31 434 1973

10 Bonnier H Simoons M L and Leuftink E Ventricular premature beats during exercise A comparison of healthy men and patients with coronary artery disease Ned Tijdschr Geneeskd 121 825 1977 (in Dutch)

11 Crawford M Rourke R O Ranakrishna H Henning M and Ross J Comparative effectiveness of exercise testing and Holter monitoring for detection of arrhythmias in patients with previous myocardial infarction Am J Cardiol 33 13? 1974

12 De Maria A N Vera Z Amsterdam E A Mason D T and Massumi R A Disturbances of cardiac rhythm and conduction induced by exercise Diagnostic prognostic and therapeutic implications Am J Cardiol 33 73? 1974

13 Irving J B and Bruce R A Exertional hypotension and postexertional ventricular fibrillation in stress testing Am J Cardiol 39 849 1977

14 McHenry P L Risks of graded exercise testing Am J Cardiol 39 935 1977

15 Haskell W L Cardiovascular complications during exercise training of cardiac patients Circulation 57 920 1978

Tocainide therapy for refractory ventricular arrhythmias

D M Roden M D
S B Reele M D *
S B Higgins Ph D
R Keith Carr M Sc
R F Smith M D
J A Oates M D *
R L Woosley M D Ph D **
Nashville Tenn.

Parenteral lidocaine is particularly effective in the acute control of ventricular ectopy in the early post myocardial infarction period However chronic oral therapy has not proven feasible in part because of a short half life of elimination In addition lidocaine undergoes extensive first pass hepatic extraction[1] leading to accumulation of the de-ethylated metabolites monoethylglycinexylidide (MEGX) and glycinexylidide (GX) these contribute to side effects during oral therapy[2] Tocainide is a congener of lidocaine (Fig 1) which has been shown to have antiarrhythmic efficacy in man[3] when given orally It is particularly suitable for long term use since absorption after oral administration is virtually complete and its long half life of elimination (12 to 22 hours) allows dosing on an eight to 12 hourly basis We report our experience with the use of tocainide in a group of patients whose complex ventricular arrhythmias could not be successfully treated with the standard therapeutic regimens

Materials and methods

Patients were studied in the coronary care unit or the Clinical Research Center of Vanderbilt University Hospital All those who had received trials of quinidine procainamide propranolol and disopyramide without satisfactory response were candidates for this trial Plasma concentrations of quinidine procainamide and propranolol were routinely monitored These agents were considered ineffective if

1 Computerized analysis of 12 to 24 hours of ECG documented lack of sustained (>60%) arrhythmia suppression and persistence of symptoms with plasma concentrations in the range usually associated with efficacy or

2 Acute intravenous or oral dosing with computerized analysis of ECG data pre and post therapy showed no change in the arrhythmia with the attainment of plasma concentrations in the usual therapeutic range or

3 Patients developed intolerable side effects with lack of suppression of their arrhythmia at lower dosages or

4 Patients developed allergic or immunologic side effects which necessitated the discontinuation of therapy or

5 Therapy with a given agent was contraindicated

From the Divisions of Clinical Pharmacology and Cardiology Departments of Medicine and Pharmacology Vanderbilt University School of Medicine Nashville Tenn

Supported by Grants from the United States Public Health Service Nos. GM 15431 and GM 07569 by a grant from the General Clinical Research Center Program of the Division of Research Resources National Institutes of Health 5M01 RR95 and by Astra Pharmaceutical Products Inc

Received for publication Oct 10 1979

Accepted for publication Jan 10 1980

Reprint requests Dr R L Woosley Division of Clinical Pharmacology Dept of Pharmacology Vanderbilt University School of Medicine Nashville Tenn 3723

*Current address Pharmacological and Clinical Investigation Unit Bronson Hospital Kalamazoo Mich.

*Dr Oates is the Joe and Morris Werthan Professor of Investigative Medicine

**Dr Woosley is the recipient of a Career Development Award in Clinical Pharmacology from the Pharmaceutical Manufacturers Association Foundation.

0002-8703/80/070015 + 08$00 80/0 © 1980 The C V Mosby Co

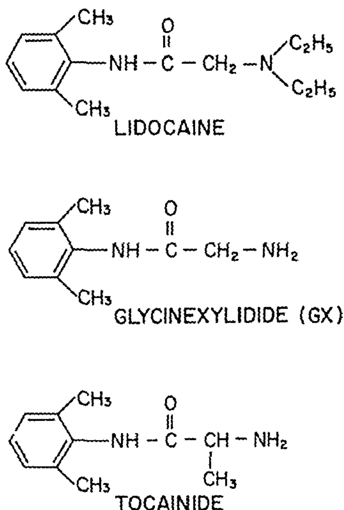


Fig 1 Chemical structures of lidocaine glycinexylidide a lidocaine metabolite and tocainide

Lidocaine responsiveness was assessed in all patients This was done either by (1) a loading infusion at 120 µg/Kg /minute for 25 minutes (15 patients) or (2) the assessment of lidocaine re sponsiveness by the review of rhythm strips and charts after standard acute therapy in a CCU setting most often 100 to 150 mg intravenously followed by an infusion of 1 to 4 mg /minute (four patients) Arrhythmias were considered respon sive to lidocaine if 90% or more ventricular ectopic depolarizations (VEDs) and all complex arrhyth mias were abolished without symptoms Such strict criteria were necessary because of the short control periods used Plasma concentrations when available were monitored with either approach

Patients with symptomatic arrhythmias resis tant to standard therapy (as described above) regardless of lidocaine response were asked to participate in the evaluation of the use of tocain ide for control of refractory ventricular arrhyth mias Patients giving informed consent were then withdrawn from other antiarrhythmic therapy (usually lidocaine) if possible After 24 to 48 hours of ECG recording while receiving placebo tocain ide was begun at low dosages (200 to 400 mg orally every 8 to 12 hours) Each dosage level was continued until steady state was achieved (36 to 48 hours) at which time 12 hour ECG tapes and plasma for trough tocainide concentration were obtained and the daily dosage was increased if necessary The dosage was increased to the point of arrhythmia suppression or the development of side effects Transient dose related side effects were controlled if possible by the adoption of lower doses at shorter dosing intervals or by the administration of medication with a meal or snack

In this highly selected group of patients chronic oral therapy with tocainide or the con ventional agents described above was declared successful if a 60% decrease in VED frequency was documented as well as suppression of symp tomatic ventricular tachycardia (VT) while the patient was ambulatory in hospital In order to avoid misinterpreting spontaneous variation in arrhythmia frequency for a drug response com parisons were made between pre drug placebo control data and all dosages of tocainide to ascertain if a dose response relationship was pres ent As well therapy with tocainide was discon tinued after the trial to detect a return to baseline arrhythmia frequency and severity in those who appeared to respond this was omitted in patients whose clinical status was felt to be too unstable to permit such a maneuver

ECG data were recorded on eight track tape using a Honeywell model 96 FM recorder Tapes were then analyzed by a blinded computer opera tor using a PDP 11/40 laboratory minicomputer and a previously described and verified program which counts VEDs and runs of VT (≥ 3 VEDs in a row rate ≥ 100/minute) using a template matching algorithm

Patients whose arrhythmia was responsive to tocainide were discharged on the dosage regimen providing maximum benefit and a minimum of side effects and were followed as out patients at weekly to monthly intervals Routine electrocar diograms hematology (Coulter counter) bio chemistry (SMAC) and antinuclear antibody (ANA) tests (Meloy Kit 6715 Electronic Drive Springfield VA) were performed at each visit

Table I Study population

	Age	*Sex*	*Type of heart disease*	*Character of arrhythmia*	*Symptoms at the time of trial*
Tocainide responsive					
1	46	M	ASCVD	VT VF	Syncope CHF
2	4[illegible]	F	Unknown	VT	Syncope stroke
3	30	F	MVP	VT	Syncope
4	69	F	ASCVD	VT	Syncope CHF
5	41	F	Cardiomyopathy	VT	DOE
6	60	F	ASCVD	VT	Syncope
7	59	M	Unknown	VT	Syncope
8	69	F	ASCVD	VT VF	Syncope
9	52	F	HHD	VEDs	Palpitations, DOE
10	60	F	Unknown	VEDs	Palpitations
11	57	M	ASCVD	VEDs	Angina CHF
12	54	F	MVP	VEDs rare VT	Syncope
13	47	M	ASCVD	VT VF	Syncope CHF
14	35	M	Cardiomyopathy	VT VF	Syncope CHF
15	60	M	ASCVD	VT	Near syncope CHF
Tocainide non responsive					
1	32	F	Unknown	VT	Syncope
2	51	M	ASCVD	VT	Palpitations
3	28	F	Unknown	VT	Syncope stroke
4	35	F	Unknown	VT	Syncope

Abbreviations ASCVD = atherosclerotic cardiovascular disease MVP = mitral valve prolapse VT = ventricular tachycardia VF = ventricular fibrillation VED = ventricular ectopic depolarization DOE = dyspnea on exertion CHF = congestive heart failure HHD = hypertensive heart disease

Emergency DC-cardioversion required in the past

Rhythm control was evaluated by 30 to 120 minute rhythm strips run at 1 0 mm /sec by periodic 24 hour Holter recording and by the presence or absence of symptoms of VT

Blood samples for determination of plasma tocainide concentration were obtained in the 30 minutes prior to a dose and 60 to 90 minutes after a dose for the assessment of plasma concentrations associated with therapeutic effects and with possible adverse effects Following the addition of glycinexylidide as an internal standard plasma was extracted into methylene chloride at an alkaline pH Aliquots were then injected into a μBondapak C column (3 9 × 300 mm) The analysis used a high performance liquid chromatograph (Waters Associates Milford Mass) the flow rate of the mobile phase (water methanol acetic acid (500 100 15 (v /v /v)) was 1 5 ml / minute at ambient temperature Eluate was monitored for UV absorption at 254 nm (spectrophotometer model 440 Waters Associates) Samples of drug free plasma to which internal standard and varying amounts (0 to 15 μg/ml) of tocainide had been added were used to prepare a standard curve relating peak height ratio (tocainide internal standard) to tocainide concentration Peak height ratios from patient samples were then used to determine tocainide concentration The coefficient of variation was 8 9 to 9 6% for concentrations ≥ 10 μg/ml at lower concentrations (≤ 5 μg/ml) it rose to 21 6 to 23% The sensitivity of this method allowed detection of concentrations of tocainide ≥ .5 μg/ml Samples from patients being treated with quinidine procainamide disopyramide phenytoin propranolol digoxin warfarin hydrochlorothiazide furosemide diazepam flurazepam aspirin and acetaminophen produced no interfering peaks Data from patients who had received lidocaine within the previous 24 hours were not used because of potential interference by GX

Results

Nineteen patients participated in this study (Table I) The ages ranged from 28 to 69 years 12 were female Eight had coronary artery disease one had hypertensive heart disease two had mitral valve prolapse and two had congestive cardiomyopathies the remaining six had ventricular arrhythmias with no identifiable heart dis-

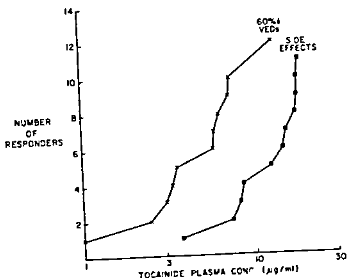


Fig 2 Relationships between the cumulative number of patients demonstrating a response (arrhythmia suppression or side effects) and tocainide concentration

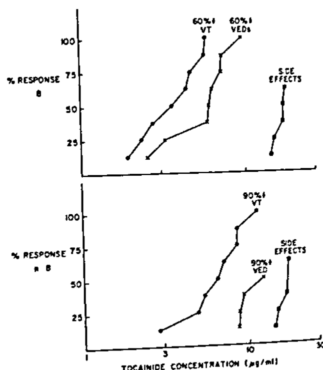


Fig 3 Dose-response relationships for VED suppression VT suppression and side effects among the eight patients with frequent VT

ease All six had normal echocardiograms QTc intervals (range 360 to 420 msec) and physical examinations Follow up ranged from 2 to 15 years and neither congestive heart failure nor angina developed in any patient Symptoms in the 19 patients ranged from palpitations to syncope cerebrovascular accidents and cardiopulmonary arrests All had frequent VEDs Fifteen had a history of ventricular tachycardia and four of these had previously documented ventricular fibrillation

Fifteen of the 19 responded to tocainide (as defined above) All 13 patients whose arrhythmia was sensitive to lidocaine were in this group while only two of the six patients resistant to lidocaine responded to tocainide ($P < 0.005$ Fisher s exact test) Lidocaine resistance was documented in four patients by the absence of change in arrhythmia frequency and by the presence of typical side effects during the infusion protocol after a mean dose of 270 mg (range 180 to 390 mg) over 25 minutes The fifth patient had no change in arrhythmia frequency and a plasma concentration of 5 8 µg/ml following the lidocaine infusion and the sixth patient was judged lidocaine resistant following review of her CCU data showing no change in arrhythmia frequency during prolonged infusions of 2 to 3 mg /minute

Dose response plots relating reduction in VED frequency (from placebo baseline) to trough tocainide concentration (at steady state) could be constructed in 12 (patients 1 to 12) responders Placebo baseline recordings were not obtained in the other three (patients 13 to 15) but tocainide was effective in abolishing their frequents runs of symptomatic VT All of these 12 patients demonstrated incremental reductions in VED frequency as the plasma concentration of tocainide increased The plot relating plasma concentration to aggregate response in the group is shown in Fig 2 a curve relating concentration to the observed incidence of side effects (see below) for the entire group of 19 patients is also shown in Fig 2. Eight of these twelve (patients 1 to 8) had frequent runs of VT (≥ 2 episodes per hour) during placebo therapy Fig 3 shows the relationship among VED reduction VT reduction and side effects in this group

Return of arrhythmia to 88%(±SE 18) of placebo control frequency was observed in 11 of the 15 responding patients (Fig 4) This maneuver was not attempted in three (patients 8 13 14) and in a fourth (patient 6) VT recurred only hours after she missed a dose of tocainide necessitating reinstitution of therapy Concurrent antiarrhythmic therapy was undertaken in two patients In one a partial response to tocainide was seen initially and a greater degree of arrhythmia control was established with the addition of

procainamide This patient had had no response to procainamide alone and so was discharged on the two agents together he subsequently died (see below) A second patient underwent tocainide dose ranging while receiving propranolol for paroxysmal atrial tachycardia She developed tremor and nausea and was not judged to have an antiarrhythmic response to tocainide Four patients were also treated with digoxin three for control of congestive heart failure and one for paroxysmal atrial fibrillation

Side effects were observed in 11 patients (58%) during tocainide therapy and most often occurred immediately following a dose taken on an empty stomach These side effects affected primarily the central nervous system (ataxia paresthesias lightheadedness nervousness and tremor) the other dose related side effects were gastrointestinal (primarily nausea) In four patients the margin between effective and excessive plasma concentrations was so narrow that out patient treatment had to be stopped

Chronic out patient therapy with tocainide was undertaken in 12 of the 15 responders three could not be discharged on drug (two developed drug allergy in hospital and one died) The discharge regimens were 800 to 2 400 mg /day (mean 1 600) in two to three divided doses Three additional deaths have occurred (see below) four patients have had to stop therapy because of prominent central nervous system side effects at effective antiarrhythmic dosages and three further cases of drug allergy have occurred Maintenance of arrhythmia control was documented at the regularly scheduled clinic visits in all patients (including those who subsequently died) symptoms previously related to the arrhythmia did not recur Two (patients 1 and 8) continue on treatment and are asymptomatic at one and four years respectively Drug withdrawal and substitution of placebo has been carried out three times over the 4 years patient 1 has been on treatment on each occasion return of ventricular tachycardia was documented

Four patients died during tocainide therapy One was a 35 year old man with a congestive cardiomyopathy who died in hospital after the initial trial of tocainide his symptomatic runs of VT were suppressed with treatment leaving isolated VEDs and couplets He died in cardiogenic shock while awaiting heart transplantation

The second patient was a 47 year old man with severe coronary artery disease and recurrent ventricular fibrillation initially controlled on tocainide Two weeks after discharge on tocainide he developed atrial tachycardia followed shortly by ventricular fibrillation that required D C cardioversion and was eventually controlled with a combination of procainamide and tocainide After a total of 3 months on tocainide while at home he developed increasing symptoms of congestive heart failure and had another cardiopulmonary arrest He was taken to his local hospital where ventricular fibrillation was documented and he could not be resuscitated Postmortem tocainide plasma concentration was in his usual therapeutic range (10 0 μg/ml) but procainamide (11 4 μg/ml) and N acetylprocainamide (19 9 μg/ml) were well above his usual levels

The third patient who died was a 52 year old woman who died suddenly at home after 5 months of therapy She had been seen in the clinic four days before with tocainide levels in her usual range and good arrhythmia control but had stopped taking her medications the day prior to her sudden death

The fourth patient was a 57 year old man with coronary artery disease and congestive heart failure He had been receiving tocainide for 13 months After developing increased angina and dyspnea at home he died suddenly autopsy

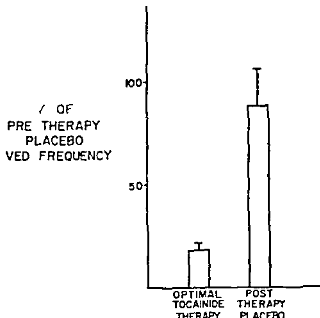


Fig 4 Comparison of VED frequency at the end of tocainide dose ranging and following tocainide withdrawal (mean ± SE)

showed a coronary artery dissection which was thought to have precipitated a fatal arrhythmia Tocainide concentration was 10 9 μg/ml post mortem

Five patients developed allergic symptoms during tocainide therapy In four these occurred within six weeks of the initial dose while a rash developed in the fifth after four months on therapy Two patients had pruritic rashes only one patient had pruritus without a rash a fourth had rash pruritus night sweats and eosinophilia and the fifth had fever and night sweats All symptoms resolved promptly with withdrawal of tocainide and in no case could other agents be implicated as a possible cause

Biochemical and hematological screening tests showed no adverse reactions during tocainide therapy One patient entered the trial with a strongly positive ANA test which had developed during procainamide therapy over the previous 8 months she was symptomatic with arthritis and pulmonary infiltrates The ANA have persisted during the year she has been taking tocainide although the symptoms and infiltrate have resolved Two other patients developed ANA shortly after starting tocainide but in both cases prior procainamide therapy could be implicated and in neither did symptoms of lupus erythematosus develop

Discussion

There is evidence that chronic therapy with beta blocking agents anti platelet agents ' or phenytoin might reduce the incidence of sudden death in a high risk population Procainamide and quinidine have been studied by Myerburg and colleagues in survivors of ventricular fibrillation maintenance of serum levels in the therapeutic range appeared to be the major determinant of the incidence of recurrent fibrillation rather than isolated VED frequency The high incidence of side effects during therapy with these agents and the question of what defines a "therapeutic concentration in this context have not yet been addressed One possibility is that while VEDs may be unchanged during adequate therapy more complex arrhythmias may be disproportionately decreased A tendency toward such a reduction was seen in the study of Myerburg and associates although statistical significance was not achieved We have recently shown that a 70% decrease in VED frequency during propranolol therapy was associated with abolition of VT [11] The similar disproportionate reduction in VT frequency as plasma concentration increased that we have now demonstrated with tocainide suggests that this phenomenon may occur often

The definition of the therapeutic window i.e., the range defined by plasma concentrations associated with effective and with excessive drug actions is arbitrary The degree of acceptable risk of side effects varies among individuals (and populations) as does the end point used to designate response (Fig 3) In this study group 25% of the 19 patients developed side effects at plasma tocainide concentrations ≥ 11 μg/ml, while 25% of those responding (with ≥ 60% VED suppression) did so at plasma concentrations ≥ 3 μg/ml (Fig 2) Thus using arbitrary 25% limits on acceptable degrees of efficacy and toxicity the range 3 to 11 μg/ml could be termed the therapeutic window for tocainide in this group

Recent observations have increased awareness of the problem of spontaneous variation in VED frequency Morganroth and colleagues' advocated use of prolonged recordings of ECG data during control and drug periods to avoid misinterpreting this spontaneous variation Virtual abolition of arrhythmias is needed to demonstrate efficacy with short periods of observation such as acute response to lidocaine However lesser changes in arrhythmia frequency may be attributed to drug treatment if longer periods of observation are undertaken The prolonged periods of observation used in this study as well as the demonstration of dose response relationships showed that tocainide had antiarrhythmic activity in these patients Re-emergence of arrhythmia during substitution of placebo for active therapy provided additional evidence that this was a true drug effect In the three patients in whom tocainide was not withdrawn the dramatic clinical improvement (no further cardic arrests) during tocainide dose ranging as well as increasing VED suppression made it unlikely that the observed response was fortuitous

Acute sequential drug testing has been proposed as an approach to the patient with serious symptomatic arrhythmias ' However translation of the results of acute drug testing to chronic oral therapy is not always possible For instance testing with intravenous propranolol for VED suppression does not predict response to oral

therapy.[14] Acute drug testing does not permit accumulation of metabolites which may have antiarrhythmic activity of their own; response to procainamide challenge does not predict subsequent response to N-acetylprocainamide.[15] We have now shown that response to acute challenge with one agent, lidocaine, predicts response to a different (although structurally related) agent, tocainide, in patients whose arrhythmias are not controlled by conventional oral drug therapy. The fact that the spectrum of side effects seen during the use of these two agents is also similar may reflect the structural similarity among lidocaine, its metabolites, and tocainide.

Trials of tocainide in populations of patients who did not exhibit the resistance to standard agents shown by this group have had a 66 to 71% response rate.[1, 17] Winkle and colleagues and Ryan and associates[19] have reported their experience with patients resistant to conventional therapy; the initial response rates were also 70%. Three of the 17 patients reported by Winkle and colleagues died on therapy. No deaths were recorded among those treated with tocainide by Ryan and co-workers, although that group also noted a high incidence (70%) of dose-related symptoms and two cases of drug-related rash (6.7%).[1, 9]

The high mortality rate in this and other reports of chronic tocainide therapy reflects the underlying severity of the rhythm disturbance and basic disease process among these highly selected groups of patients. It may also be that reduction in VED (or VT) frequency does not decrease the risk for sudden death despite an association between the two. However, even during short periods of therapy, these highly selected patients often note improvement in other VED-related symptoms such as dyspnea on exertion or recurrent syncope. In such patients, the only clinically attainable end point may be suppression of symptoms even after systematic trials of multiple conventional and investigational agents.[1]

Trials of new antiarrhythmic agents in this setting are biased by the referral and selection processes. The true place of tocainide in the therapy of ventricular arrhythmias and sudden death prophylaxis is not yet known. It provided long-term life-saving treatment in two of our 19 patients. In this population of patients with resistant arrhythmias, the use of tocainide was associated with a good initial response rate but a narrow toxic therapeutic ratio and a high incidence of drug allergy which limited therapy in many patients.

Summary

Tocainide, a congener of lidocaine, was used to treat symptomatic ventricular arrhythmias in 19 patients resistant to or unable to tolerate conventional agents. In this highly selected group, 15 showed good initial responses to oral therapy. Ventricular tachycardia was suppressed to a greater extent than isolated ventricular ectopic depolarizations at any plasma concentration, and upward dose ranging showed progressive suppression of both. Arrhythmia responsiveness to lidocaine was found to be an excellent predictor of tocainide response.

Of the 15 responders, one died 24 hours after stopping therapy, three died while receiving tocainide, nine stopped because of adverse reactions (five allergic), and two continue on therapy at 1 and 4 years. We conclude that tocainide is an effective agent for the short-term suppression of ventricular arrhythmias, particularly ventricular tachycardia sensitive to lidocaine, but a high incidence of adverse effects limits its application to chronic therapy in many patients.

REFERENCES

1. Boyes RN, Scott DB, Jebson PJ, Godman MJ, and Julian DG: Pharmacokinetics of lidocaine in man. Clin Pharmacol Ther 12:102, 1971.
2. Strong JM, Parker M, and Atkinson AJ Jr: Identification of glycinexylidide in patients treated with intravenous lidocaine. Clin Pharmacol Ther 14:67, 1973.
3. McDevitt DG, Nies AS, Wilkinson GR, Smith RF, Woosley RL, and Oates JA: Antiarrhythmic effects of a lidocaine congener, tocainide, 2-amino-2',6'-propionoxylidide, in man. Clin Pharmacol Ther 19:396, 1976.
4. Lalka D, Meyer MB, Duce BR, and Elvin AT: Kinetics of the oral antiarrhythmic lidocaine congener tocainide. Clin Pharmacol Ther 19:757, 1976.
5. Higgins SB, Woosley RL, Herrin B, Compton JL, and Harris TR: A minicomputer based system for the quantification of ventricular arrhythmias. Computers in Cardiology 1978. IEEE Computer Society, Long Beach, 1979, pp 355.
6. Furberg CD, and Friedewald WT: The effects of chronic administration of beta blockade on long-term survival following myocardial infarction, *in* Beta Adrenergic Blockade: A New Era in Cardiovascular Medicine. Braunwald E, ed. Proceedings of International Symposium. Excerpta Medica, New York, 1978, pp 171-177.
7. The Anturan Reinfarction Trial Research Group: Sulfinpyrazone in the prevention of cardiac death after myo-

cardial infarction The Anturane Reinfarction Trial N Engl J Med 298 289 1978
8 Vajda F J E Prineas R J Lovell R R H and Sloman J G The possible effect of long term high plasma levels of phenytoin on mortality after acute myocardial infarction Europ J Clin Pharmacol 5 138 1973
9 Myerburg R J Conde C Sheps D S Appel R A Kiem I Sung R J and Castellanos, A Antiarrhythmic drug therapy in survivors of prehospital cardiac arrest Comparison of effects on chronic ventricular arrhythmias and recurrent cardiac arrest Circulation 59 855 1979
10 Jelinek M V Lohrbauer L and Lown B Antiarrhythmic drug therapy for sporadic ventricular ectopic arrhythmias Circulation 49 659 1974
11 Woosley R L Kornhauser D Smith R Reele S Higgins S B Nies A S Shand D G and Oates J A Suppression of chronic ventricular arrhythmias with propranolol Circulation 60 819 1979
12 Morganroth J Michelson E L Horowitz L N Josephson M E Pearlman A S and Dunkman W B Limitations of routine long term electrocardiographic monitoring to assess ventricular ectopic frequency Circulation 58 408 1978
13 Lown B and Graboys T B Management of patients with malignant ventricular arrhythmias Am J Cardiol 39 910 1977
14 Woosley R L Reele S Kornhauser D Shand D and Oates J A Lack of correlation between antiarrhythmic efficacy of intravenous and oral propranolol Circulation 58(Suppl II) 248 1978
15 Woosley R L Roden D M Reele S B Smith R F Wilkinson G R and Oates J A Comparative clinical pharmacology of procainamide and N acetylprocainamide (Acecainide) Circulation 60(Suppl. II) 323 1979
16 Woosley R L McDevitt D G Nies A S Smith R F Wilkinson G R and Oates J A Suppression of ventricular ectopic depolarizations by tocainide Circulation 56 980 1977
17 Winkle R A Meffin P J Fitzgerald J W and Harrison D C Clinical efficacy and pharmacokinetics of a new orally effective antiarrhythmic tocainide Circulation 54 884 1976
18 Winkle R A Meffin P J and Harrison D C Long term tocainide therapy for ventricular arrhythmias Circulation 57 1008 1978
19 Ryan W Engler R LeWinter M and Karliner J S Efficacy of a new oral agent (Tocainide) in the acute treatment of refractory ventricular arrhythmias Am J Cardiol 43 285 1979
20 Engler R Ryan W LeWinter M Bluestein H and Karliner J S Assessment of long term antiarrhythmic therapy Studies of the long term efficacy and toxicity of tocainide Am J Cardiol 43 612 1979
21 Winkle R A Alderman E L Fitzgerald J W and Harrison D C Treatment of recurrent symptomatic ventricular tachycardia Ann Intern Med 85 1 1976

IMPORTANT
INFORMATION FOR AUTHORS

Effective June 1 1980 all manuscripts for the AMERICAN HEART JOURNAL should be sent to

Dean T Mason M D
Section of Cardiovascular Medicine
University of California
School of Medicine
Davis California 95616

The electrophysiologic effects of intravenous lidocaine in the Wolff-Parkinson-White syndrome

Peter A Barrett M D F R A C P
Michael M Laks M D
William J Mandel M D
Iwao Yamaguchi M D
Los Angeles Calif

In spite of the progress in our understanding of the pathophysiology of the Wolff Parkinson White syndrome since its description in 1930 [1] knowledge of the most appropriate medical therapy is still inadequate Clinically it is difficult to assess therapy in the Wolff Parkinson White syndrome as the tachycardias are variable and paroxysmal [1] and because patients may historically overstate or understate the incidence of palpitations [2, 8] Knowledge is accumulating however with the increasing number of electrophysiologic assessments of the effects of therapy in this syndrome [9]

Isolated clinical case reports[1] have indicated that intravenous lidocaine may be effective therapy for supraventricular tachyarrhythmias with accessory pathway conduction Lidocaine in fact has been reported as being extremely valuable [1, 2] in this regard because of a depressant effect on accessory pathway conduction Such supraventricular tachyarrhythmias may resemble ventricular tachyarrhythmias which may also occur in the WPW syndrome [5, 8] and lidocaine is known to be effective therapy for these [3] Accordingly in an acute situation differentiation between supraventricular tachyarrhythmias with accessory pathway conduction and ventricular tachyarrhythmias may be academic The purpose of this study therefore was to obtain an electrophysiologic assessment of lidocaine in the WPW syndrome

Material

Twelve patients with the WPW syndrome were studied One had coronary heart disease and another had Ebstein s anomaly There were 10 males The ages of the patients ranged from 15 to 63 years with a mean of 33 ± 5 years (mean ± standard error of the mean) Seven patients had Type A[3] WPW syndrome and in one of these the WPW anomaly was intermittent Five patients had Type B[32] WPW syndrome Tachycardia had been present in all patients for a mean of 11 ± 3 years with a mean frequency of approximately monthly occurrence

Methods

The studies were performed in the fasting state after obtaining informed consent The patients had not received any medication for at least 48 hours prior to study Intracardiac electrograms were obtained by standard techniques [33] and were recorded on a multichannel photographic recorder with paper speeds between 25 and 100 mm / sec (Electronics for Medicine Model DR 12) Multiple standard electrocardiographic leads were recorded with high right atrial low right atrial coronary sinus and His bundle electrograms The protocol used was as previously described [13, 31]

During sinus rhythm the heart rate and P delta AH and HV intervals were measured High right atrial pacing[1] was performed at

From the Divis n of Cardiology Department of Medicin Cedars-Sinai Medical Cente the Dep tment of Cardiology Harbor General Hospital and the Departm nt of Medicin UCLA School of Medicine Los Ang les C lif

Supported in part by National Institutes of Health Grant No HL 17651

Rece ved f r p blicat on Oct 19 1979

A cepted fo publ catio Jan 17 1980

Reprint equests Publicat ns Office Divis n of Card ology Cedars Sinai Medical Center 8700 Beverly Blvd Los Angeles Calif 90048

0002-8 /03/80/070023 + 11$01 10/0 © 1980 The C V Mosby Co

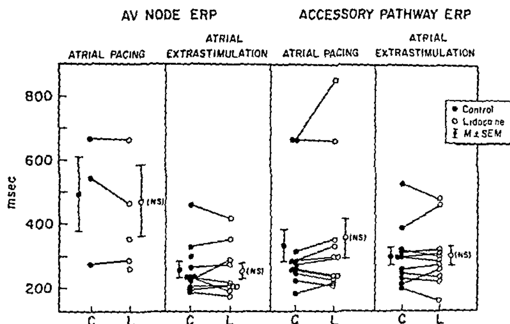


Fig 1 Anterograde AV effective refractory period *(ERP)* of the AV node and the accessory pathway as determined by the atrial pacing and extrastimulus techniques Statistical analysis (*NS* = no significant change) relates only to those cases where determinations were able to be made in both the control state *(C)* and after lidocaine *(L)* Results are expressed as mean ± standard error of the mean

rates to assess anterograde AV refractoriness A measurement of anterograde AV node effective refractory period was obtained by taking the cycle length of the maximum rate of atrial pacing where 1 1 AV node conduction was preserved The anterograde accessory pathway effective refractory period was taken as the cycle length of the maximum rate of atrial pacing where 1 1 accessory pathway conduction was preserved The atrial extra stimulus technique[35, 36] during atrial pacing was used to determine the antero grade AV node and accessory pathway effective refractory periods and the atrial muscle effective refractory period Right ventricular apical pacing was performed at increasing rates to assess ventriculoatrial (VA) conduction The VA conduction time was measured from the ventricular stimulus artifact to the onset of the right septal atrial, coronary sinus and high right atrial electrograms A measurement of the VA effective refractory period was taken as the cycle length of the maximum rate of ventricular pacing where 1 1 VA conduction was preserved The ventricular extrastimulus technique during ventricular pacing was used to determine the VA and the ventricular muscle effective refractory periods

The initiation of tachycardia by these maneuvers[34, 40] was noted The rate and VA conduction time in the case of re entry tachycardia and the shortest RR interval of the ventricular response in the case of atrial fibrillation were measured

The above procedures were repeated with the catheters in the same positions after an intravenous bolus of lidocaine 1 mg/kg administered over 30 seconds The repeat studies begun 1 minute after the bolus were completed in all patients within 15 minutes Statistical evaluation was performed with Student s t test for paired samples

Results

Effective refractory periods

Anterograde AV node effective refractory period The anterograde AV node effective refractory period was able to be determined by means of the atrial pacing technique in only three patients in the control state and in five after lidocaine This was because 1 1 accessory pathway conduction usually persisted at the maximum rate of atrial pacing with 1 1 AV conduction The point of failure of 1 1 AV node conduction therefore could not be readily determined as the His deflection was then obscured in the ventricular depolarization wave of the His bundle electrogram In three patients therefore the mean anterograde AV node effective refractory period as determined by this technique decreased by 5% after lidocaine from 495 ± 116 msec to

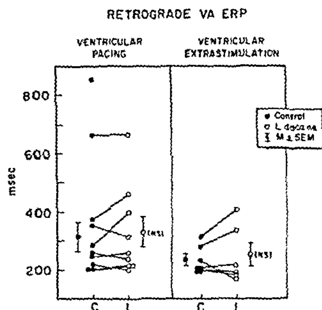


Fig 2 Retrograde VA effective refractory period *(ERP)* as determined by the ventricular pacing and extrastimulus techniques

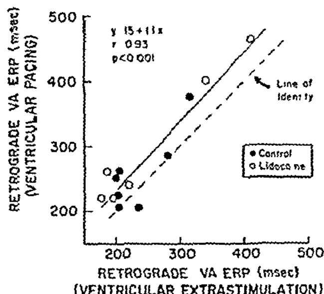


Fig 3 Linear relationship close to the line of identity between the retrograde VA effective refractory period *(ERP)* as determined by the ventricular pacing and extrastimulus techniques

472 ± 110 msec without statistical significance (p = 0 5) (Fig 1)

The anterograde AV node effective refractory period was able to be determined by means of the atrial extrastimulus technique in 10 patients in the control state and after lidocaine In two patients with increasing prematurity of atrial extrastimuli in the control state accessory pathway conduction persisted to the point of failure of AV conduction In these cases the point of failure of AV node conduction could not be readily determined as the His deflection was obscured In these 10 patients therefore the mean anterograde AV node effective refractory period as determined by this technique decreased by 1% after lidocaine from 258 ± 26 msec to 256 ± 25 msec without statistical significane (p = 0 9) (Fig 1)

Anterograde accessory pathway effective refractory period The anterograde accessory pathway effective refractory period was able to be determined by means of the atrial pacing technique in 11 patients in the control state and after lidocaine In one patient with intermittent WPW syndrome delta were not present at the time of the study In these 11 patients the mean anterograde accessory pathway effective refractory period as determined by this technique increased by 7% after lidocaine from 334 ± 51 msec to 359 ± 63 msec without statistical significance (p = 0 2) (Fig 1)

In these 11 patients the mean anterograde accessory pathway effective refractory period as determined by the atrial extrastimulus technique increased by 1% after lidocaine from 302 ± 28 msec to 305 ± 29 msec without statistical significance (p = 0 8) (Fig 1)

Retrograde VA effective refractory period The retrograde VA effective refractory period was able to be determined by means of the ventricular pacing technique in 10 patients in the control state and nine after lidocaine One to one VA conduction was absent at all rates of ventricular pacing in one patient in the control state and in two after lidocaine so that the exact value of the VA effective refractory period could not be determined in these instances The technique was not performed in another patient In nine patients therefore the mean retrograde by 6% after lidocaine from 314 ± 49 msec to 332 ± 51 msec without statistical significance (p = 0 3) (Fig 2)

The retrograde VA effective refractory period was able to be determined by means of the ventricular extrastimulus technique in seven patients in the control state and in six of these patients after lidocaine It was not performed in the three instances of absent 1 1 VA conduction or in two other instances In six patients there

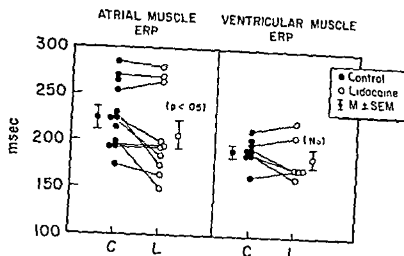


Fig 4 Atrial and ventricular muscle effective refractory periods (FRP) as determined by the extrastimulus technique

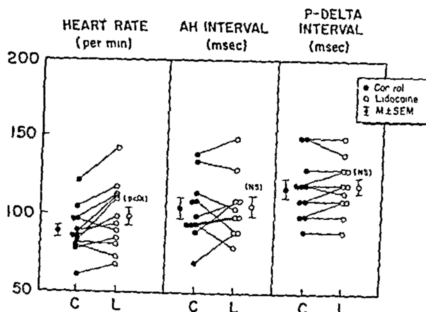


Fig 5 Heart rate and anterograde AV conduction times (*AH* and *P delta* intervals) during sinus rhythm

fore the mean VA effective refractory period as determined by this technique increased by 6% after lidocaine from 240 ± 19 msec to 254 ± 40 msec without statistical significance ($p = 0.6$) (Fig 2)

The retrograde VA effective refractory period was estimated by both the ventricular pacing and extrastimulus techniques in 13 instances in the control state and after lidocaine There was a significant linear correlation between the two techniques ($r = 0.93$ $p < 0.001$) and the line drawn from the linear regression equation was close to the line of identity (Fig 3)

Atrial and ventricular muscle effective refractory periods The atrial muscle effective refractory period was determined by means of the atrial extrastimulus technique in 12 patients in the control state and in 10 after lidocaine In 1 patients therefore the mean atrial muscle effective refractory period significantly decreased by 8% after lidocaine from 226 ± 11 msec to 208 ± 15 msec ($p = 0.04$) (Fig 4)

The ventricular muscle effective refractory period was determined by means of the ventricular extrastimulus technique in eight patients in the control state and in six after lidocaine In six patients therefore the mean ventricular muscle effective refractory period decreased by 3% after lidocaine from 193 ± 7 msec to 188 ± 10 msec without statistical significance ($p = 0.5$) (Fig 4)

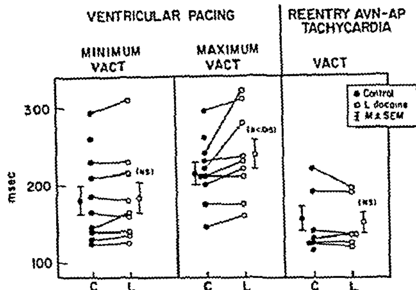


Fig 6 Retrograde VA conduction time (CT) during ventricular pacing (minimum and maximum) and during reentry AV node accessory pathway tachycardia

Conduction times The mean heart rate of the 12 patients significantly increased by 11% after lidocaine from 89 ± 4/minute to 99 ± 6/minute (p = 0 01) (Fig 5)

Anterograde AV node conduction time The AH interval or the anterograde AV node conduction time was able to be determined during sinus rhythm in 11 patients in the control state and in 10 after lidocaine In three instances the His deflection was obscured in the delta wave of the His bundle electrogram In 10 patients therefore the mean anterograde AV node conduction time during sinus rhythm increased by 2% after lidocaine from 105 ± 7 msec without statistical significance (p = 0 7) (Fig 5)

Anterograde accessory pathway conduction time The P delta interval an estimate of the anterograde accessory pathway conduction time was able to be determined during sinus rhythm in all patients in the control state and after lidocaine except for the patient in whom delta waves were absent at the time of study In 11 patients therefore the mean anterograde accessory pathway conduction time during sinus rhythm increased by 2% after lidocaine from 118 ± 6 msec to 120 ± 5 msec without statistical significance (p = 0 5) (Fig 5)

Retrograde VA conduction time In nine patients the mean minimum VA conduction time at the slowest rate of ventricular pacing with 1 1 VA conduction increased by 2% after lidocaine from 181 ± 19 msec to 184 ± 20 msec without statistical significance (p = 0 2) (Fig 6) The mean maximum VA conduction time at the maximum rate of ventricular pacing with 1 1 VA conduction significantly increased by 11% after lidocaine from 214 ± 13 msec to 238 ± 19 msec (p = 0 03) (Fig 6)

During the studies re entry AV node accessory pathway tachycardia with anterograde AV node and retrograde accessory pathway conduction developed in seven patients in the control state and in six after lidocaine In six patients therefore the mean retrograde accessory pathway conduction time during re entry AV node accessory pathway tachycardia decreased by 3% after lidocaine from 155 ± 16 msec to 150 ± 14 msec without statistical significance (p = 0 3) (Fig 6)

Tachycardia initiation

Incidence and rate of tachycardia Re entry AV node accessory pathway tachycardia was initiated in seven patients in the control state and in six after lidocaine In six patients therefore the mean rate of the tachycardia increased by 2% after lidocaine from 196 ± 10/minute to 200 ± 9/minute without statistical significance (p = 0 4) (Fig 7)

Re entry accessory pathway AV node tachycardia with anterograde accessory pathway and retrograde AV node conduction was initiated in one patient in both the control state and after lidocaine The rate of the tachycardia remained unchanged at 207/minute (Fig 7)

Atrial fibrillation with accessory pathway con

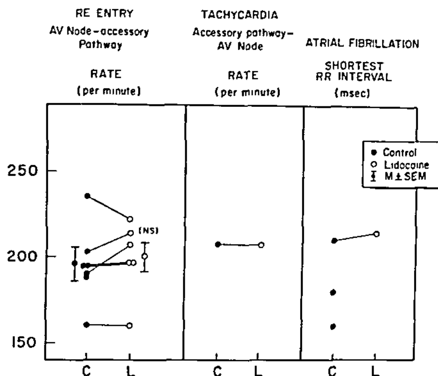


Fig 7 Incidence and rate of tachycardias initiated during the electrophysiologic studies

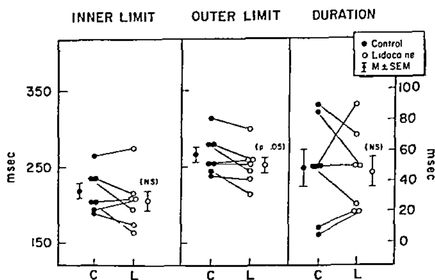


Fig 8 Features of the "tachycardia zone" or the zone of atrial extrastimuli that initiate reentry tachycardia

duction developed in three patients in the control state and in one of these after lidocaine In the latter patient the shortest RR interval of the ventricular response increased by 2% after lidocaine from 210 msec to 215 msec (Fig 7)

Tachycardia zone Re entry tachycardia of either type was initiated by atrial extrastimuli in seven patients in the control state and after lidocaine The tachycardia zone or the zone of coupling intervals of atrial extrastimuli that initiate tachycardia may be described in terms of its inner and outer limits and its duration The mean inner limit of the tachycardia zone decreased by 6% after lidocaine from 219 ± 10 msec to 206 ± 13 msec without statistical significance (p = 0 2) The mean outer limit significantly decreased by 5% after lidocaine from 267 ± 10 msec to 253 ± 10 msec (p = 05) The mean duration of the tachycardia zone decreased by 6% after lidocaine from 49 ± 12 msec to 46 ± 10 msec without statistical significance (p = 0 8) (Fig 8)

Anterograde accessory pathway AV node effective refractory period difference. The difference between the anterograde accessory pathway and AV node effective refractory periods has been implicated as a factor in the tendency to develop re-entry tachycardia.[10] This relationship is illustrated in Fig. 9. It resembles a parabola with an optimal anterograde accessory pathway AV node effective refractory period difference for the initiation of re-entry tachycardia by atrial extrastimuli in these patients of approximately 40 msec. When this difference is less than or greater than approximately 40 msec, tachycardia initiation by atrial extrastimuli becomes progressively less likely. Where this value could be calculated, it was removed from its optimal value by 25 ± 3 msec in the control state (10 patients) and by 26 ± 6 msec after lidocaine (nine patients).

Discussion

In most cases tachycardia in the WPW syndrome occurs on the basis of a re-entry circuit formed by the atrial muscle, the AV node, the His-Purkinje system and ventricular muscle, and the accessory pathway. ⁴ Its direction is usually anterograde (across the AV node accessory pathway tachycardia) so that the QRS complexes are normal, but occasionally it is reversed (re-entry accessory pathway AV node tachycardia) so that the QRS complexes are bizarre, consisting of pure delta waves. Occasionally atrial fibrillation and flutter may occur, generally with accessory pathway conduction, so that the QRS complexes are usually bizarre.[5] Rarely ventricular fibrillation and sudden death may occur, being more likely in those patients with paroxysmal atrial fibrillation. Even the former tachycardias, however, may produce significant hemodynamic impairment requiring urgent therapy. Moreover, (1) re-entry AV node accessory pathway tachycardia may be conducted with aberrant intraventricular conduction and so may resemble ventricular tachycardia, (2) atrial fibrillation with accessory pathway conduction may also resemble ventricular tachycardia if the irregular ventricular response characteristic of atrial fibrillation is not noted, and (3) re-entry accessory pathway AV node tachycardia and atrial flutter with accessory pathway conduction and a regular ventricular response may be indistinguishable from ventricular tachycardia.

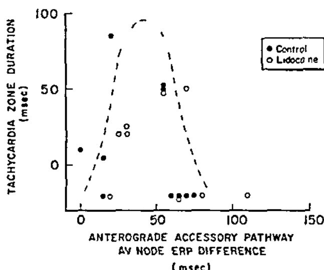


Fig. 9. Parabolic relationship between the difference in the anterograde effective refractory periods *(ERP)* of the accessory pathway and the AV node and the duration of the tachycardia zone. A tachycardia zone duration of 0 means that there was only one coupling interval of atrial extrastimuli that initiated reentry tachycardia. Points below this are instances where there was no tachycardia initiation by atrial extrastimuli.

Lidocaine is known to be effective in ventricular tachyarrhythmias ' and has been said to be extremely valuable in the WPW syndrome for supraventricular tachyarrhythmias with accessory pathway conduction, ' suggesting that lidocaine should be administered in either case. Nevertheless, as the tachycardias of the WPW syndrome are variable and paroxysmal, it is difficult to ascribe to the administration of a drug what may have occurred spontaneously. Because of this and because of possible additional effects of lidocaine, this electrophysiologic study was undertaken.

For a drug to be effective intravenously as acute therapy for the tachycardias of the WPW syndrome, it should act on part or all of the re-entry circuit in one or both directions so as to (a) terminate or decrease the rate of the re-entry tachycardias or (b) decrease the rate of the ventricular response in atrial fibrillation and flutter in the case of depression of the accessory pathway, or it should act on the atrial or ventricular muscle in such a way as to terminate atrial fibrillation or flutter or ventricular fibrillation.

Anterograde AV conduction. Lidocaine did not significantly increase the mean anterograde effective refractory periods of the AV node or the accessory pathway as determined by atrial pacing or extrastimulation. Accordingly, it is not likely to terminate the re-entry tachycardias by

this mechanism or decrease the rate of the ventricular response in atrial fibrillation

Rosen and colleagues[9] reported an increase in the anterograde accessory pathway effective refractory period as determined by atrial pacing in four of six patients and as determined by atrial extrastimulation in one of two patients after the intravenous administration of lidocaine in doses similar to those used in our patients Some of our patients also developed an increase in the antero grade accessory pathway effective refractory peri od after lidocaine but a decrease was just as likely and there was no way of predicting a favorable response

Lidocaine did not significantly increase the mean anterograde conduction time across the AV node or the accessory pathway during sinus rhythm Accordingly it is not likely to decrease the rate of the re-entry tachycardia by this mechanism

Retrograde VA conduction We have previous ly found [1] and it is again in evidence in these patients that the atrial pacing technique overes timates the anterograde AV node effective refrac tory period as compared to the atrial extrastimu lus technique but that no such disparity exists in the case of the determination of the anterograde accessory pathway effective refractory period We attribute the disparity in the former case to the parasympathetic effects of rapid atrial pacing [5] which increase the AV node but not the accesso ry pathway effective refractory period [3] We feel that these considerations also apply in the reverse direction with ventricular pacing In this study in the determination of the VA effective refracto ry period there was excellent linear correlation between the techniques of ventricular pacing and extrastimulation and the linear regression equa tion fell close to the line of identity This suggests that it was in fact the retrograde accessory pathway effective refractory period that was determined as opposed to the retrograde AV node effective refractory period Lidocaine did not sig nificantly increase the mean retrograde accessory pathway effective refractory period as deter mined by ventricular pacing or extrastimulation Accordingly it is not likely to terminate re entry AV node accessory pathway tachycardia by this mechanism

Ruskin and co workers reported the effects of intravenous lidocaine 1 mg/kg as a bolus and 4 mg/minute by infusion on retrograde VA conduction in patients without the WPW syndrome As determined by the ventricular extrastimulus technique the mean retrograde His Purkinje system effective refractory period in four patients significantly decreased by ≥ 13% after lidocaine from 324 ± 20 msec to 281 ± 31 msec ($p < 0.005$) There were variable effects on the retrograde AV node effective refractory period in 11 patients Lidocaine would appear unlikely to terminate re entry accessory pathway AV node tachycardia by this mechanism

Lidocaine did not significantly increase the minimum retrograde accessory pathway conduc tion time during ventricular pacing at the slowest rates with 1 1 VA conduction There was a signif icant increase in the maximum retrograde acces sory pathway conduction time during ventricular pacing at maximum rates with 1 1 VA conduc tion suggesting that lidocaine may prolong the retrograde accessory pathway conduction time in re entry AV node accessory pathway tachycar dia and so decrease its rate Nevertheless such an effect was not manifest in the six patients who developed this tachycardia in the control state and after lidocaine where there was no significant change in the retrograde accessory pathway con duction time

Atrial and ventricular muscle refractoriness Lidocaine significantly decreased the mean atrial muscle effective refractory period with no signif icant change in the mean ventricular muscle effective refractory period Accordingly it is not likely to terminate the re-entry tachycardias by this mechanism A decrease in the atrial muscle effective refractory period may in fact facilitate the development or continuation of atrial fibrilla tion

Tachycardia initiation

Incidence and rate of tachycardia As intrave nous lidocaine had minimal or no effect on the effective refractory periods of the components of the re entry circuit in either direction it was not surprising that re entry tachycardia was initiated during electrophysiologic study in a similar num ber of patients in the control state and after lidocaine Furthermore as it had minimal or no effect on the conduction time across the compo nents of the re-entry circuit in either direction it was not surprising that there was no significant change in the rates of the tachycardias ini tiated

No specific attempt was made to initiate atrial

fibrillation by atrial pacing at very rapid rates During the course of the routine studies however atrial fibrillation occurred in three patients in the control state and in one of these after lidocaine In this patient the shortest RR interval of the ventricular response was minimally increased The shortest RR interval of the ventricular response correlates with the anterograde accessory pathway effective refractory period [35, 36] and in the two remaining patients the anterograde accessory pathway effective refractory period as determined by the atrial extrastimulus technique decreased by 4% and 20% Accordingly should atrial fibrillation have occurred after lidocaine in these two patients there would have been no increase and perhaps even a decrease in the shortest RR interval of the ventricular response

Tachycardia zone The initiation of re entry tachycardia by atrial extrasystoles may be expected to be less likely when the range of coupling intervals of atrial extrastimuli that initiate re entry tachycardia is found to be small Lidocaine did not significantly decrease the duration of this tachycardia zone If the outer limit of the tachycardia zone is decreased an atrial extra systole with a coupling interval at this outer limit will no longer initiate re entry tachycardia Lidocaine was successful in significantly reducing this tachycardia zone outer limit but only by 5%

Anterograde accessory pathway AV node effective refractory period difference When the anterograde accessory pathway effective refractory period is relatively great and the anterograde AV node effective refractory period is relatively small there is strong likelihood of an atrial extrasystole finding the accessory pathway refractory and the AV node available for conduction and therefore for the initial event of the re entry AV node accessory pathway circuit to occur Completion of this circuit however requires that retrograde accessory pathway conduction be intact and if in any way the retrograde effective refractory period of the accessory pathway parallels the anterograde effective refractory period such conduction will not occur Theoretically therefore it appears that there is an optimal accessory pathway AV node effective refractory period difference for initiation of re entry tachycardia by atrial extrasystoles when both the anterograde and retrograde limbs of the re entry circuit are considered together Such a relationship has already been reported [37] and appeared to be present in our cases The anterograde accessory pathway AV node effective refractory period difference was as far removed from this optimal value for tachycardia initiation in both the control state and after lidocaine Thus tachycardia initiation by atrial extrasystoles was just as likely after lidocaine as before

Clinical implications A number of aspects of the WPW syndrome were not able to be assessed by these studies These include any possible effects of intravenous lidocaine on the atrial or ventricular muscle in such a way as to prevent the extrasystoles which initiate the other arrhythmias Any such action however is not of relevance in the assessment of intravenous lidocaine as acute therapy for tachycardia that is already present Any possible effect of intravenous lidocaine on the atrial or ventricular muscle in such a way as to terminate atrial fibrillation or flutter or ventricular fibrillation likewise was not studied The significant decrease in the mean atrial muscle effective refractory period however may be expected to maintain rather than terminate atrial fibrillation

As intravenous lidocaine 1 mg/kg did not significantly depress conduction in either direction in any part of the re-entry circuit studied or alter features related to tachycardia initiation intravenous bolus administration of lidocaine is most unlikely except in isolated unpredictable cases to terminate or decrease the rate of the re entry tachycardias or to decrease the rate of the ventricular response in atrial fibrillation in patients with WPW syndrome Nevertheless larger doses than routinely used may produce transient bypass blockade

Summary

Twelve patients with the Wolff Parkinson White syndrome underwent electrophysiologic study before and after the bolus intravenous administration of lidocaine 1 mg/kg There was no significant increase in the effective refractory period of the anterograde AV node pathway the anterograde or retrograde accessory pathway or the atrial or ventricular muscle intravenous bolus administration of lidocaine is unlikely to terminate the re entry tachycardias or decrease the rate of the ventricular response in atrial fibrillation in the WPW syndrome There was no significant increase in the anterograde or retrograde AV conduction times bolus

of lidocaine is unlikely to decrease the rates of the re entry tachycardias In addition lidocaine failed to alter significantly features related to tachycardia initiation Except in isolated unpredictable cases intravenous bolus administration of lidocaine is not likely to be of benefit in the supraventricular tachyarrhythmias of the WPW syndrome

The authors wish to acknowledge the art work of Mr Lance Laforteza and the secretarial assistance of Ms Terry Collett

REFERENCES

1 Wolff L. Parkinson J and White P D Bundle branch block with short PR interval in healthy young people prone to paroxysmal tachycardia AM HEART J 5 685 1930
2. Averill K H., Fosmoe R. J and Lamb L. E Electrocardiographic findings in 67,375 asymptomatic subjects, Am J Cardiol. 6 108 1960
3 Wolff L. Wolff Parkinson White syndrome Historical and clinical features, Progr Cardiovasc Dis 2 677 1960
4 Smith R F The Wolff Parkinson White syndrome as an aviation risk Circulation 29 672 1964
5 Chung K Y., Walsh T J and Massie E Wolff Parkinson White syndrome AM HEART J 69 116 1965
6 Berkman N L. and Lamb L. E The Wolff Parkinson White electrocardiogram A followup study of 5-28 years N Engl J Med 278 492 1968
7 Isaeff D M Gasten J H and Harrison D C Wolff Parkinson White syndrome Long term monitoring for arrhythmias JAMA 222 449 1972
8 Hindman M C., Last, J H., and Rosen K M Wolff Parkinson White syndrome observed by portable monitoring Ann Intern Med 79 654 1973
9 Rosen, K M., Barwolf C., Ehsani, A., and Rahimtoola S H Effects of lidocaine and propranolol on the normal and anomalous pathways in patients with pre-excitation Am J Cardiol 30 801 1972
10 Wellens H J J and Durrer D Effect of digitalis on atrioventricular conduction and circus movement tachycardia in patients with the Wolff Parkinson White syndrome Circulation 47 1229 1973
11 Mandel W J Lak M M., Clifton J., Hayakawa H., and Fink B Tachycardia in Wolff Parkinson White syndrome Alterations by ouabain and procainamide (Abstract) Clin Res 21 435 1973
12. Wellens H J J and Durrer D Effect of procaine amide quinidine and ajmaline in the Wolff Parkinson White syndrome Circulation 50 114 1974
13 Spurrell R A J Krikler D M and Sowton E Effects of verapamil on electrophysiologic properties of anomalous atrioventricular connexion in Wolff Parkinson White syndrome Br Heart J 36 256 1974
14 Spurrell R A J Thorburn C W and Camm J Effects of disopyramide on electrophysiological properties of specialized conduction system in man and on accessory atrioventricular pathway in Wolff Parkinson White syndrome Br Heart J 37 861 1975
15 Mandel W J., Lak M M Obayashi K Hayakawa H and Daley W The Wolff Parkinson White syndrome Pharmacological effect of procainamide AM HEART J 90 744 1975
16 Wellens H J J., Lie K I., Bar F W., Wesdorp J C Dohmen H J Duren D R. and Durrer D Effect of amiodarone in the Wolff Parkinson White syndrome Am J Cardiol 38 189 1976
17 Denes P Wu D and Amat y Leon F The effect of propranolol on anomalous pathway refractoriness and circus movement tachycardia in patients with pre-excitation (Abstract) Am J Cardiol 39 319 1977
18 Sellers T D Campbell R W F., Bashore T M and Gallagher J J Effects of procainamide and quinidine sulfate in the Wolff Parkinson White syndrome Circulation 55 15 1977
19 Dye C L Atrial tachycardia in Wolff Parkinson White syndrome Conversion to normal sinus rhythm with lidocaine Am J Cardiol 24 265 1969
20 Josephson M E., Kastor J A and Kitchen, J G Lidocaine in Wolff Parkinson White syndrome with atrial fibrillation Ann. Intern Med 84 44 1976
21 Chung E K Tachyarrhythmias in Wolff Parkinson White syndrome Antiarrhythmic drug therapy JAMA 237 376 1977
22 Chung E K Wolff Parkinson White syndrome Current views, Am J Med. 62 252 1977
23 Langendorf R Lev M., and Pick R Auricular fibrillation with anomalous AV excitation (WPW syndrome) imitating ventricular paroxysmal tachycardia Acta Cardiol 7 241 1952
24 Herrmann, G R Oates J R and Range T M Paroxysmal pseudoventricular tachycardia and pseudoventricular fibrillation in patients with accelerated A-V conduction AM HEART J 53 254 1957
25 Wolff L Anomalous atrioventricular excitation (Wolff Parkinson White syndrome) Circulation 19 14 1959
26 Kaplan M A., and Cohen K L Ventricular fibrillation in the Wolff Parkinson White syndrome Am J Cardiol 24 259 1969
27 Dreifus L S Haiat R., and Watanabe Y Ventricular fibrillation A possible mechanism of sudden death in patients with Wolff Parkinson White syndrome Circulation 43 520 1971
28 Coskey R L and Danzig R Cardiac arrest due to extreme tachycardia with Wolff Parkinson White syndrome West J Med 120 319 1974
29 Weiss W A Intravenous use of lidocaine for ventricular arrhythmias Anesth. Anag 39 369 1960
30 Harrison D C., Sprouse J H and Morrow A G The antiarrhythmic properties of lidocaine and procainamide Circulation 28 486 1963
31 Frieden J Lidocaine as an antiarrhythmic agent AM HEART J 70 713 1965
32 Rosenbaum F F., Hecht H H Wilson F N and Johnston F D The potential variations of the thorax and the esophagus in anomalous atrioventricular excitation (Wolff Parkinson White syndrome) AM HEART J 29 281 1945
33 Scherlag B J Lau S. H., Helfant R H Berkowitz W D., Stein E., and Damato A N A catheter technique for recording His bundle activity in man Circulation 39 13 1969
34 Damato A. N Lau S H., Helfant R H., Stein E Berkowitz W D and Cohen S I Study of atrioventricular conduction in man using electrode catheter recordings of His bundle activity Circulation 39 287 1969
35 Damato A N., Lau, S H., Patton R D Steiner C., and Berkowitz W D A study of atrioventricular conduction in man using premature atrial stimulation and His bundle recordings Circulation 40 61 1969
36 Wit A L. Weiss M B., Berkowitz W D Rosen K M Steiner C and Damato A N Patterns of atrioventricular

ular conduction in the human heart Circ Res 27 315 1970
37 Goldreyer B N and Bigger J T Ventriculoatrial conduction in man Circulation 41 935 1970
38 Durrer D Schoo L and Schuilenburg R M The role of premature beats in the initiation and termination of supraventricular tachycardia in the Wolff Parkinson White syndrome Circulation 36 644 1967
39 Narula O S Wolff Parkinson White syndrome A review Circulation 47 872 1973
40 Durrer D and Wellens H J J The Wolff Parkinson White syndrome anno 1973 Eur J Cardiol 1/4 34 1974
41 Mandel W J Laks M M Obayashi K and Bilder J Prolongation of the tachycardia zone A possible mechanism for medical failure in paroxysmal supraventricular tachycardia Eur J Cardiol 3/2 117 1975
42 Bishop L F Bundle branch block with short RR intervals in individuals without organic heart disease Am J Med Sci 194 794 1937
43 Hunter A Papp C and Parkinson J The syndrome of short RR interval apparent bundle branch block and associated paroxysmal tachycardia Br Heart J 2 107 1940
44 Littmann D Tarnower H Wolff Parkinson White syndrome Am Heart J 32 100 1946
45 Wolff L and White P D Syndrome of short PR interval with abnormal QRS complexes and paroxysmal tachycardia Arch Intern Med 82 446 1948
46 Curry P V L and Krikler D M Atrial fibrillation in the Wolff Parkinson White syndrome Br Heart J 37 779 1975
4 Dreifus L S Wellens H J J and Watanabe Y Sinus bradycardia and atrial fibrillation associated with the Wolff Parkinson White syndrome Am J Cardiol 38 149 1976
48 Bleifer S Kahn M and Grishman A Wolff Parkinson White syndrome A vectorcardiographic electrocardiographic and clinical study Am J Cardiol 4 321 1959
49 Burchell H B Surgical approach to the treatment of ventricular pre excitation Adv Intern Med 16 43 1970
50 Wallace A G Boineau J P and Dandon R M WPW syndrome A new look Am J Cardiol 28 509 1971
51 Barrett P A Jordan J L Mandel W J Yamaguchi I and Laks M M The electrophysiological effects of intravenous propranolol in the Wolff Parkinson White syndrome Am Heart J 98 213 1979
52 Lange G Action of driving stimuli from intrinsic and extrinsic sources on in situ cardiac pacemaker tissues Circ Res 17 449 1965
53 Clifton J Mandel W J Laks M M and Hayakawa H Effects of alterations in autonomic tone on AV conduction in the Wolff Parkinson White (WPW) syndrome Circulation 46(Suppl II) II 109 1972
54 Rinkin J N Damato A N Akhtar M and Foster J R Effect of lidocaine on retrograde refractory periods in patients with normal intraventricular conduction (Abstract) Am J Cardiol 39 290 1977
55 Castellanos A Myerburg R and Craparo K Factors regulating ventricular rates during atrial flutter and fibrillation in pre excitation (Wolff Parkinson White) syndrome Br Heart J 35 811 1973
56 Wellens H J J and Durrer D Wolff Parkinson White syndrome and atrial fibrillation Relation between refractory period of accessory pathway and ventricular rate during atrial fibrillation Am J Cardiol 34 777 1974
57 Mandel W J Yamaguchi I and Laks M M Syndromes of accelerated conduction Prac Cardiol 3 72 1977

Rheumatic mitral stenosis cross-sectional echocardiographic analysis

Masahito Naito M D
Joel Morganroth M D
T Joseph Mardelli M D
Chin C Chen M D
Leonard S Dreifus M D
Philadelphia Pa

Whereas M mode echocardiography proved valuable in recognizing the presence of rheumatic mitral valvular disease[1-3] its limitations in assessing the severity of the process and predicting the hemodynamic findings are well recognized[4] In contrast cross sectional echocardiography images the mitral valve apparatus from several tomographic views[5-11] and allows an assessment of mitral valve orifice size The use of the short axis view has been applied extensively to estimate the mitral valve orifice size with excellent correlation with hemodynamic data[5-13] More recently the technical difficulties in imaging the actual mitral orifice using this view have been recognized[14-16] The longitudinal left ventricular cross sectional echocardiographic view has been primarily used to recognize rheumatic mitral valvular involvement However its role in predicting the segmental anatomy and the severity of stenosis has not been fully explored The purpose of this study was to assess the specific role of the longitudinal left ventricular view in predicting the severity of rheumatic mitral stenosis and to define the spectrum of rheumatic stenosis of the mitral valvular apparatus

Materials and methods

The control population of 22 normal individuals (mean age 51 ± 10 years 55% female) identified by catheterization were selected to determine the normal mitral valve morphology and leaflet motion Twenty one patients with rheumatic mitral stenosis with no or with mild mitral regurgitation and having both hemodynamic and cross sectional echocardiographic studies within a four week period constituted the study population Their mean age was 61 ± 12 years with 76% females

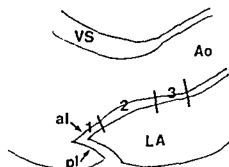


Fig 1 A schematic of the left ventricular longitudinal cross-sectional echocardiographic view demonstrating the ventricular septum *(VS)* aorta *(Ao)* left atrium *(LA)* and the anterior *(al)* and posterior *(pl)* mitral valve leaflets The anterior leaflet was divided into its tip *(1)* body *(2)* and base *(3)*

Cross sectional echocardiographic views were obtained by the methods outlined by Kisslo and associates[5] and by Silverman and co workers[7]

All cross sectional echocardiographic studies were obtained using a wide angle 84 degree commercially available phased array system (Varian V 3000) with a transducer containing 32 mounted piezoelectric crystals with a diameter of 1 3 × 1.2 inches at the skin level All studies were recorded on video tape (Sanyo) and were later reviewed in real time slow motion and frame by frame analysis Individual frame selection for figures were

From the Department of Research and Medicine of the Lankenau Hospital and the Department of Medicine of the Jefferson Medical College of the Thomas Jefferson University Philadelphia Pa

Received for publication N 19 9
Accepted for publication Jan 10 1980

Reprint requests Joel Morganroth M D Associate Director Cardiology Lankenau Hospital 2 1 Medical Science Bldg Philadelphia Pa 1 1

0002-8 03/80/070034 + 07$00 70/0 © 1980 The C V Mosby Co

photographed using a Polaroid camera The quality of these still frame images was significantly graded since only one half of the line density was present during the still framing M mode echocardiographic studies were obtained using a Smith Kline Echoline 20A with a 2 25 MHz transducer Left ventricular longitudinal and short axis views of the mitral valve were obtained using the conventional approach[1] The left ventricular longitudinal view was considered adequate when both mitral leaflets were visualized and the continuity of the anterior mitral leaflet with posterior aortic root and the interventricular septum with anterior aortic root were preserved The anterior mitral leaflet was analyzed in all 22 control individuals to define the normal range of mitral valvular motion in diastole Subsequently the mobility of the anterior mitral leaflet in diastole in the study group could be analyzed The anterior mitral leaflet was arbitrarily divided into three portions tip body and base The tip was defined as the leading edge of the anterior mitral leaflet The base of the leaflet was considered that portion of the leaflet near and at its attachment to the annulus The body of the leaflet was defined as that part between the tip and the base (Fig 1) The short axis view involved multiple tomographic sections starting at the level of the aortic valve and progressing downwards to the level of the mitral valve and then to the papillary muscles and apex The short axis view of the mitral valve orifice size was considered adequate only when the multiple tomographic views could be identified in succession and the mitral orifice size could be confidently assessed at the tip of the valve rather than a skewed view off of the true orifice (Fig 2) Gain settings were carefully adjusted as previously recommended The apical four chamber view was considered adequate when the atrioventricular valves and all four chambers were well visualized

All cross sectional echocardiographic studies were analyzed by two independent observers

The mobility of the anterior mitral leaflet was considered normal (as in controls) when the leaflet moved freely and its tip approximated the interventricular septum during diastole In the study group the tip of the leaflet demonstrated restricted motion due to commissural fusion producing a convex appearance towards the interventricular septum during diastole This doming

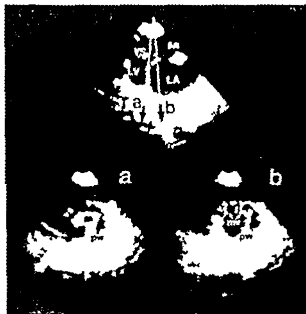


Fig 2 The top cross sectional echocardiogram reveals a left ventricular longitudinal view demonstrating the ventricular septum ( ) left ventricular cavity (LV) aorta (Ao) and left atrium (LA) The two superimposed white lines (a b) show the planes in which the short axis views labeled *a* and *b*" (below) were derived The short axis view labeled *a* depicts the mitral valve orifice at the mitral valve tip whereas the short axis view labeled *b* depicts the apparent mitral valve (mv) orifice size when the echocardiographic beam was skewed off of the mitral valve tip View a represents the actual mitral valve orifice area in this patient with mitral stenosis whereas a normal mitral valve orifice area would have been predicted if the estimation was made using view b which was obtained off of the tip of the mitral valve *pw* = posterior left ventricular wall

effect was estimated as severe (Fig 3A) if the convexity of the leaflet was striking and collided with the interventricular septum in diastole and was considered mild to moderate (Fig 3B) if the convexity of the anterior leaflet did not approximate the septum

End systolic frames were analyzed for the presence of mitral valve prolapse pattern namely a leaflet position beyond the mitral ring toward the left atrium at end systole

Severity of mitral stenosis was defined using hemodynamic findings Mitral valve orifice size was measured using Gorlin's formula Severe mitral stenosis was considered present when valve orifice size was less than 1 cm moderate between 1 and 1 5 cm and mild when more than 1 5 cm Left ventriculography was performed in the right anterior oblique view and the mitral valve was analyzed for any systolic prolapse in this view using the criteria of Cohen and associates[1]



Fig 3 The left ventricular longitudinal cross sectional echocardiographic view in *panel A* represents severe doming of the anterior mitral valve leaflet *(small white arrow)* The ventricular septum *(VS)* aorta *(Ao)* and left atrium *(LA)* are also shown *Panel B* demonstrates mild to moderate anterior mitral valve leaflet doming

Table I Correlation of the pattern of anterior mitral leaflet motion and severity of mitral stenosis

Pattern of anterior mitral leaflet motion by cross sectional longitudinal view		*Severity based on catheterization findings*		
		Mild	*Moderate*	*Severe*
Pattern A (N = 8)	Mild moderate doming (N = 2)	1	1	0
	Severe doming (N = 6)	2	2	2
Pattern B (N = 8)		0	1	7
Pattern C (N = 5)		0	0	5

Results

I Patterns of anterior mitral leaflet motion in diastole The anterior mitral leaflet could be adequately analyzed in all 21 patients with mitral stenosis Three patterns of leaflet motion were identified (Table I and Fig 4)

Pattern A Restricted motion of the leaflet s tip with doming of the whole leaflet was seen in eight patients Mild to moderate doming was noted in two of eight and severe doming was noted in six of eight Hemodynamic data identifying severe mitral stenosis were noted in only two of eight patients all of whom had severe diastolic doming of the anterior leaflet

Pattern B Restricted motion of the leaflet s tip and body with mild doming of the basal portion of the leaflet was seen in eight patients Fig 4 demonstrates this pattern, showing that the base of the leaflet is moving during the cardiac cycle while the tip and body have restricted motion Hemodynamically severe mitral stenosis was present in seven of these eight patients

Pattern C Restricted motion of the entire leaflet was seen in 5 patients all of whom had hemodynamically severe mitral stenosis Fig 4 shows an example of this pattern of severely restricted leaflet motion during systole and diastole

Thus the pattern of echocardiographic longitudinal view of the anterior leaflet motion correlated well with the hemodynamic severity of the mitral stenosis However a close correlation was not always observed in Pattern A (Fig 5)

II Extent of thickening of the anterior mitral leaflet Table II details the extent of thickening of the anterior mitral leaflet and the correlation with the degree of hemodynamic severity Five patients had no thickening of the anterior mitral leaflet while three showed thickening involving primarily the tip ten involving the tip and body and three involving the entire leaflet Patients with valvular thickening were on the average a decade older than those without thickening (Table II) The extent of thickening correlated with the severity of mitral stenosis (Table II) Thus the spread of thickening of the mitral anterior leaflet appeared to extend from tip and body towards the base When the leaflet was not thickened or only thickened at its tip the frequency of severe mitral stenosis was less than if the leaflet s body or the entire leaflet was thickened



Fig 4 These three left ventricular longitudinal cross sectional echocardiographic views were obtained from three different patients with mitral stenosis, and show the observed patterns of anterior mitral valve leaflet motion *Panel A* demonstrates doming of the anterior mitral valve leaflet *(white arrow)* with leaflet thickening isolated to the tip *Panel B* shows thickening primarily of the tip and body with relative sparing of the base of the mitral valve leaflet *(single white arrow)* *Panel C* demonstrates little anterior mitral valve leaflet motion with severe thickening of the tip body and base *Ao* = aorta *LV* = left ventricle *LA* = left atrium and *IVS* = ventricular septum

III Patterns of anterior mitral leaflet in systole Mitral valve prolapse pattern was noted in three of eight patients with Pattern A leaflet motion All three patients showed severe doming of the anterior mitral leaflet (Fig 6) and two of these three had hemodynamic evidence of severe mitral stenosis The posterior mitral leaflet was not prolapsed in any of these three patients nor did left ventriculography reveal prolapse in any patient Mitral valve prolapsing motion can be seen with rheumatic mitral stenosis (Fig 6) but appears to require a pliable anterior leaflet with severe commissural fusion and doming The presence of mitral valve prolapse pattern by cross sectional echocardiography suggested hemodynamically severe mitral stenosis The lack of posterior leaflet prolapse (Fig 6) suggested that the anterior leaflet prolapse is unrelated to the floppy valve syndrome but probably was a systolic rebound phenomenon of the markedly domed leaflet motion in diastole

Discussion

The limitations of M mode echocardiography in assessing the severity of mitral stenosis are recognized The recent introduction of cross sectional echocardiography has enhanced the ability to estimate the severity of the rheumatic process and can actually image the true orifice size of the mitral valve Henry and associates were the first to document an excellent correlation between the mitral valve area as estimated by hemodynamic data and short axis cross sectional echocardiographic imaging of the mitral orifice size However the following potential limitations to this technique are varying orifice size due to different gain settings cross sectional short axis view of the mitral valve skewed from the true orifice inability to assess subvalvular contribution due to valvular obstruction and lack of standardization of the measurement of the orifice area

The value of the longitudinal view obtained by cross sectional echocardiography has not been fully explored as a means to assess the severity of mitral stenosis Since the entire length of the mitral leaflet is visualized by this view different features of leaflet motion and thickening may reflect different hemodynamic alterations In this study we have attempted to define the spectrum of cross sectional echocardiographic findings of

Table II Extent of thickening of the anterior mitral leaflet in mitral stenosis

Number of patients	*Mean age (yrs SD)*	*Site of thickening*			*Catheterization proven severe MS*
		Tip	*Body*	*Base*	
5	5[illegible] ± 15	–	–	–	1/5
3	66 ± 15	+	–	–	1/3
10	62 ± 10	+	+	–	9/10
3	63 ± 3	+	+	+	3/3

Symbol – = no thickening + = thickening MS = mitral stenosis



Fig 5 A comparison of the left ventricular longitudinal views from two patients *(top panels)* with the short axis tomographic views *(bottom panels)* are shown Patient A demonstrated severe doming of the anterior mitral valve leaflet comparable to the degree of doming seen in patient B *(upper right hand panel)* The short axis view of the mitral valve orifice in each of these patients taken at the tip of the mitral valve revealed that although patients A and B had similar severe doming of the anterior mitral valve leaflet on the longitudinal view their mitral valve orifice areas were substantially different Patient A had a 1 1 cm and patient B had a 2 2 m mitral valve orifice area VS = ventricular septum PW = posterior left ventricular wall LA = left atrium Ao = aorta LV = left ventricle

the rheumatic mitral valvular involvement using this view

The anterior mitral leaflet motion pattern as [illegible] the longitudinal cross sectional echocardiographic view was useful in estimating the [illegible] of mitral stenosis When [illegible] was present there was loss of [illegible] tip of the anterior mitral leaflet [illegible] of the leaflet was still pliable [illegible] during diastole showing a [illegible] the interventricular septum [illegible] doming was dependent on two fact[illegible] the pliability of the mitral anterior leaflet a[illegible] extent of commissural fusion Thus with [illegible] ural fusion there was less leaflet dom[illegible] the hemodynamic severity of the stenosis [illegible] also less In contrast anterior mitral leaflet [illegible] showing severe doming correlated more [illegible] with severe mitral stenosis especially when the leaflet abutted against the interventricular septum Severe anterior leaflet doming by the longitudinal view did not always predict however the severity of mitral stenosis (Fig 5)

When the extent of thickening of the anterior mitral leaflet was analyzed it was evident that thickening tended to occur in older patients that the tip of the leaflet was the site of the earliest thickening and that the thickening tended to spread from tip towards the base Heavily thickened leaflets with basilar involvement tended to have mitral annular calcification The extent of thickening of the anterior mitral leaflet predicted the severity of mitral stenosis especially when the entire leaflet was thickened and no doming motion was seen

The occurrence of mitral valve prolapse in the presence of mitral stenosis has been previously observed [21] Nichol and colleagues found that 60% of their patients with mitral stenosis did show a systolic prolapsing pattern of the anterior mitral leaflet Others have found that mitral valve prolapse in mitral stenosis was uncommon and that the presence of both entities was merely the coexistence of two separate disease entities Our study is in support of the findings of Nichol and associates as we encountered systolic mitral leaflet prolapse in 30% of our patients with Pattern A which was correlated with the severity of leaflet doming and the degree of stenosis This suggested that the prolapse motion as seen in patients with a pliable anterior mitral leaflet occurs when the tip is restricted in motion due to commissural fusion and the body prolapses in systole as a rebound phenomenon of the markedly domed leaflet in diastole The lack of posterior mitral leaflet prolapse in these patients by echocardiography and left ventriculography suggested further that this prolapsing pattern is unrelated to the floppy valve syndrome

In conclusion the anterior mitral leaflet motion pattern on longitudinal cross sectional echocardiography may help predict the hemodynamic severity of mitral stenosis The thickening of the mitral leaflet in rheumatic disease appears to spread from leaflet tip to base and appears to involve the annulus only when the entire leaflet is thickened Mitral valve prolapse appears in patients with rheumatic mitral stenosis when the anterior leaflet is pliable and severely domed and is probably a rebound phenomenon in systole of the diastolic domed leaflet



Fig 6 Diastolic *(Diast)* and systolic *(Syst)* left ventricular longitudinal cross sectional echocardiographic views are presented from a single patient with mitral stenosis. The diastolic view demonstrates severe doming of the anterior mitral valve leaflet *(heavy white arrow)* which in systole becomes mitral valve prolapse *(small white arrow)* as a rebound phenomenon The posterior mitral valve leaflet is not prolapsed AO = aorta LA = aorta LA = left atrium VS = ventricular septum

Summary

Twenty one patients with rheumatic mitral stenosis diagnosed by both M mode echocardiography and hemodynamic findings were subjected to detailed cross sectional echocardiographic studies The age of the patients ranged from 27 to 79 years with 76% females Left ventricular longitudinal short axis and apical four chamber cross sectional echocardiographic views were obtained in each patient Three predominant patterns of anterior mitral leaflet motion on left ventricular longitudinal view were observed and correlated with the severity of mitral stenosis Pattern A (eight patients) with diastolic leaflet doming and restricted leaflet tip motion Pattern B (eight patients) with restricted tip and body leaflet motion and Pattern C (five patients) with the entire leaflet motion restricted Mitral valve prolapse as a rebound phenomenon was observed in three patients who had marked leaflet doming in Pattern A and two had severe obstruction The longitudinal cross sectional echocardiography was superior to the apical view in assessing the diastolic doming motion of the anterior mitral leaflet Thus longitudinal cross sectional echocardiographic analysis of the pliability and degree of doming of the anterior mitral leaflet is valuable in estimating the severity of mitral stenosis

REFERENCES

1 Zaky A Nasser W K and Feigenbaum H A study of mitral valve action recorded by reflected ultrasound and its application in the diagnosis of mitral stenosis Circulation 37 789 1968
2 Joyner C R Reid J M and Bond J P Reflected ultrasound in the assessment of mitral valve disease Circulation 27 503 1963
3 Gustafson A Correlation between ultrasound cardiography hemodynamics and surgical findings in mitral stenosis Am J Cardiol 19 32 1967
4 Cope C D Kisslo J A Johnson M L, and Behar V S A reassessment of the echocardiogram in mitral stenosis Circulation 52 664 1975
5 Nanda N C Gramiak R and Shah P M Echocardiographic misdiagnosis of the severity of mitral stenosis (Abstract) Clin Res 23 199A 1975
6 King D L Cardiac ultrasonography cross sectional ultrasonic imaging of the heart Circulation 47 843 1973
7 Bom N Lancee C T van Zwieten G Kloster F E and Roelandt J Multiscan echocardiography I Technical description Circulation 48 1066 1973
8 Griffith J M and Henry W L A sector scanner for real time two-dimensional echocardiography Circulation 49 1147 1974
9 Kisslo J Von Ramm O T and Thurstone F L Clinical Echocardiography Philadelphia 1978 F A Davis Company p 21
10 Sahn D J William D E Shackelton S and Friedman W F The validity of structure identification of cross sectional echocardiography J Clin Ultrasound 2 201 1974
11 Tajik A J Hager D J and Lie J T Two-dimensional real time ultrasonic imaging of the heart and great vessels Technique image orientation structure identification and validation Mayo Clin Proc 53 271 1978
12 Henry W L Griffith J M Michaelis L L McIntosh C L Morrow A G and Epstein S E Measurement of mitral orifice area in patients with mitral valve disease by real time two-dimensional echocardiography Circulation 51 827 1975
13 Wann L S Weyman A E Feigenbaum H Dillon J C Johnston K W and Eggleton R C Determination of mitral valve area by cross sectional echocardiography Ann Intern Med 88 337 1978
14 Feigenbaum H Echocardiography Philadelphia 1976 Lea & Febiger p 113
15 Kotler M N and Segal B L Clinical Echocardiography Philadelphia 1978 F A Davis Company p 344
16 Martin R P Pakrowski H Kleiman J H, Beaver W London E and Popp R L Reliability and reproducibility of two-dimensional echocardiographic measure

ment of the stenotic mitral valve orifice area Am J Cardiol 43 560 1979
17 Kisslo J Von Ramm O T and Thurstone F L Cardiac imaging using a phased array ultrasound system II Clinical technique and application Circulation 53 262 1976
18 Silverman N H and Schiller N B Apex echocardiography a new method for detecting congenital heart disease using an 80 degree phased array real time two dimensional sector scanner (Abstract) Am J Cardiol 39 266 1977
19 Gilbert B W Schatz R A Von Ramm O T Behar V S and Kisslo J A Mitral valve prolapse Two dimensional echocardiographic and angiographic correlation Circulation 54 716 1976
20 Gorlin R and Gorlin S G Hydraulic formula for calculation of the area of the stenotic mitral valve other cardiac valves and central circulatory shunts, Am. Heart J 41 1 1951
21 Cohen M V Shah P K and Spindola Franco H. Angiographic echocardiographic correlation in mitral valve prolapse Am Heart J 97 43 1979
22 Nichol P M Gilbert B W and Kisslo J A Two dimensional echocardiographic assessment of mitral stenosis Circulation 55 120 1977
23 Weinrauch L A McDonald D G., De Silva R A, Hawkins, E T Lelaud O S and Shubrooks, S J Mitral valve prolapse in rheumatic mitral stenosis, Chest 72 752 1977
24 Byron B and Kerber R Does mitral prolapse occur in mitral stenosis? (Abstract) Am. J Cardiol. 43 267 1979

Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978 Therefore all manuscripts must be accompanied by the following written statement signed by one author The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C V Mosby Company in the event the work is published The undersigned author warrants that the article is original is not under consideration by another journal and has not been previously published I sign for and accept responsibility for releasing this material on behalf of any and all co authors Authors will be consulted when possible regarding republication of their material

Pathology of the heart in acromegaly: anatomic findings in 27 autopsied patients

J T Lie MD FACC
Stanley J Grossman
Rochester Minn

As a disease entity acromegaly was first described by Marie in 1886.[1] Cardiac enlargement and congestive heart failure were added to the symptom complex of acromegaly by Huchard in 1895 and by Fournier in 1896. Although cardiomegaly is a common finding in acromegaly its pathogenesis remains obscure after numerous studies and much scrutiny by various investigators in the last 50 years. The proposed etiologic factors of cardiac enlargement in acromegaly include hypertension coronary artery disease valvular heart disease compensatory hypertrophy secondary to increased work load induced by generalized splanchnomegaly and somatomegaly and direct humoral effects of the growth hormone. A specific entity of heart muscle disease in acromegaly (acromegalic cardiomyopathy) has also been suggested by some investigators. Postmortem findings of the heart in acromegaly are surprisingly scarce since the autopsy information was available in only a fraction of patients in most published large series of cases. In this report we review the cardiac pathology of 27 autopsy cases of acromegaly seen in a single institution over a 60 year period and compare our morphologic findings with those described in the literature.

Patients and methods

We reviewed a total of 41 autopsy cases of acromegaly culled from the Mayo Clinic autopsy records of 1919 to 1978 but only 27 cases with adequate clinical data and complete postmortem examination were included in this study comprising 16 males and 11 females. The mean age of the 27 patients at death was 50 years (range = 13 to 83 years). All but four patients died before 1960. The diagnosis of acromegaly was almost exclusively clinical because radioimmunoassay of plasma growth hormone is a relatively recent procedure.

All 27 patients had the characteristic acromegalic appearance including broad hands feet and digits which had increased in size with progression of the disease and often required larger gloves shoes and rings. Prominent jaw coarse facial features visual disturbances (especially bitemporal hemianopia) and persistent headache were also common clinical findings.

The gross specimens and histologic sections of the hearts of all 27 patients were available for review. *Significant coronary atherosclerosis* was defined as one or more vessels with 75% or greater cross sectional area luminal narrowing. *Significant aortic atherosclerosis* was defined as the abdominal aorta showing 50% or greater surface area involvement by atherosclerosis. The patient's organ weights were compared with the expected weights of organs according to the body weight or the body height. Expressing the expected organ weight as 100% the patient's organ weights were calculated as a percentage of the expected weights by the formula Actual Weight/Expected Weight × 100%. All existing and newly cut additional histologic sections of the hearts were evaluated with no prior knowledge of the heart size or the patient's clinical data. Histological diagnosis of myocardial hypertrophy was made independently of whether or not the heart weight was above the expected weight.

From the Department of Pathology and Anatomy Mayo Clinic and Mayo Medical School Rochester Minn.
Received for publication Dec 6 1979
Accepted for publication Jan 29 1980
Reprint requests J T Lie M D Dept of Pathology and Anatomy Mayo Clinic Rochester Minn 55901

Mr Grossman is a fourth year student at the Mayo Medical School

0002 8703/80/0 0041 + 1 $01 90/0 © 1980 The C V Mosby Co

Table 1 Summary of major clinical and pathologic findings in 27 cases of acromegaly

Case	Sex and age (yr) at death	HT[1]	Clinical heart disease[2]	Body wt and body length	Actual organ wt and percent of normal wt in parenthesis				CAD	Aortic disease	Myocardial disease[3]	Cause of death
					Liver	Spleen	Kidneys	Heart				
Group I (11 patients with less than 10 year history of acromegaly)												
1	F 36	–	–	50 kg 161 cm	1830 g (125%)	260 g (217%)	330 g (115%)	265 g (100%)	–	–	MH IF	Post-op hypophysectomy
2	F 51	–	–	52 kg 157 cm	1510 g (106%)	135 g (113%)	350 g (12[illegible]%)	275 g (107%)	–	–	MH IF CI	Post-op hypophysectomy
3	F 22	–	–	62 kg 163 cm	2315 g (161%)	570 g (475%)	455 g (158)	190 g (71%)	–	–	–	Post op hypophysectomy
4	F 33	+	–	68 kg 173 cm	2190 g (150%)	28[illegible] g (235%)	345 g (120%)	340 g (119%)	–	–	MH IF SVD	Post-op hypophysectomy
5	M 13	+	–	81 kg 184 cm	3015 g (166%)	275 g (145%)	495 g (158%)	345 g (99%)	–	–	MH CI	Post-op hypophysectomy
6	F 34	–	–	85 kg 166 cm	1810 g (124%)	201 g (168%)	384 g (133%)	400 g (146%)	–	–	MH IF MC	Post-op hypophysectomy
7	M 46	+	MR MS CHF	102 kg 190 cm	4050 g (220%)	365 g (252%)	636 g (203%)	379 g (106%)	–	–	MH IF SVD	Carcinoma of stomach
8	F 41	–	–	80 kg 170 cm	1540 g (107%)	1[illegible]0 g (125%)	235 g (82%)	310 g (97%)	–	–	MH IF	Post-op hypophysectomy
9	F 69	–	AR CHF	77 kg 173 cm	1325 g (96%)	152 g (138%)	270 g (94%)	410 g (143%)	–	–	MH IF	Post op hypophysectomy
10	F 35	–	–	68 kg 176 cm	2492 g (171%)	193 g (161%)	503 g (17[illegible])	3[illegible]1 g (110%)	–	–	MH IF CI	Post-op hypophysectomy
11	M 44	–	–	114 kg 170 cm	2000 g (109%)	225 g (155%)	535 g (171%)	600 g (187%)	–	–	MH CI	Post-op thyroidectomy
Group II (16 patients with more than 10 year history of acromegaly)												
12	M 51	–	AR AS CHF	76 kg 180 cm	2095 g (114%)	200 g (138%)	360 g (115%)	1300 g (370%)	–	+	MH IF MC	Congestive heart failure
13	M 73	+	AF CHF	60 kg 169 cm	2075 g (150%)	145 g (100%)	415 g (133%)	550 g (172%)	–	+	MH IF SVD	Carcinoma of lung
14	F 67	+	Old MI	52 kg 162 cm	1350 g (98%)	120 g (109%)	280 g (97%)	405 g (152%)	–	–	MH IF MC	Stroke
15	M 5[illegible]	+	Old MI CHF	86 kg 172 cm	2870 g (191%)	310 g (214%)	5[illegible]5 g (177%)	775 g (238%)	+	+	MH IF CI SVD	Congestive heart failure
16	M [illegible]3	+	AP CHF Old MI	85 kg 171 cm	2000 g (145%)	400 g (276%)	3[illegible]5 g (120%)	725 g (224%)	+	+	MH IF MC	Congestive heart failure
1[illegible]	M 64	–	–	108 kg 200 cm	3040 g (175%)	790 g (545%)	–	480 g (127%)	–	–	MH IF CI	Pyelonephritis, uremia
18	M 6[illegible]	–	Old MI	[illegible]7 kg 1[illegible]2 cm	2110 g (121%)	180 g (124%)	540 g (1[illegible]3%)	495 g (1[illegible]2%)	–	–	MH IF CI	Glioblastoma
19	M 35	–	–	64 kg [illegible] cm	2250 g (123%)	400 g (255%)	47[illegible] g (152%)	4[illegible]0 g (118%)	–	–	MH IF MC SVD	Hydrocephalus
20	M 36	–		91 kg 1[illegible] cm	22[illegible]3 g (123%)	533 g (344%)	513 g (164%)	485 g (147%)	–	–	–	Post-op hypophysectomy
21	F 63	+	AR CHF	[illegible] kg 1[illegible] cm	2104 g (152%)	510 g (464%)	570 g (198%)	575 g (198%)	–	–	MH IF CI	Post-op thyroidectomy

HT = hypertension defined as blood pressure recordings ≥ 160/95 mm Hg

AF = atrial fibrillation AR = aortic regurgitation AS = aortic stenosis CHF = congestive heart failure MI = myocardial infarction MR = mitral regurgitation MS = mitral stenosis

[3]CAD = significant coronary artery disease defined as one or more extramural coronary arteries with ≥ 75% cross-sectional luminal narrowing

Abdominal aorta with ≥ [illegible] surface area involvement by atherosclerosis

[5]CI = cellular (lymphomononuclear) infiltration IF = interstitial fibrosis MC = myocarditis MH = myocardial hypertrophy SVD = small vessel disease of intramural branches of coronary arteries

Table I cont'd

Case	Sex and age (yr) at death	HT	Clinical heart disease*	Body wt and body length	Actual organ wt and percent of normal wt in parenthesis				CAD	Aortic disease	Myocardial disease*	Cause of death
					Liver	Spleen	Kidneys	Heart				
Group II cont'd												
22	M 44	+	CHF	100 kg 168 cm	2892 g (157%)	235 g (169%)	410 g (131%)	653 g (218%)	–	–	MH IF	Post-op hypophysectomy
23	M 47	–	CHF	86 kg 169 cm	3100 g (168%)	125 g (80%)	4 5 g (159%)	525 g (165%)	–	–	MH IF	Post-op thyroidectomy
24	M 81	+	–	90 kg 195 cm	1960 g (142%)	230 g (159%)	390 g (125%)	560 g (149%)	+	+	MH IF SVD	Pulmonary embolism
25	F 83	+	MR MS	48 kg 158 cm	1335 g (113%)	135 g (123%)	280 g (97%)	400 g (219%)	–	+	MH IF MC	Stroke
26	M 50	+	CHF	73 kg 172 cm	2583 g (140%)	316 g (218%)	473 g (151%)	473 g (146%)	–	–	MH IF MC	Post-op vocal cord polypectomy
27	M 40	–	–	73 kg 176 cm	1962 g (107%)	19 g (136%)	300 g (96%)	310 g (93%)	–	–	MH IF CI	Pulmonary embolism

Results

We assigned the 27 autopsy cases arbitrarily into two groups according to the duration of the disease. Group I comprised 11 patients who died within 10 years of clinical onset of acromegaly. Group II comprised 16 patients who died 10 or more years after the onset of acromegaly. The major clinical and pathologic findings are summarized in Table I.

Cause of death. Of the group I patients, nine had hypophysectomy and one had thyroidectomy; all of these 10 patients died in the first postoperative week from surgical complications. The remaining and the sole nonsurgical group I patient died of carcinoma of the stomach. Only two of the 11 (18.2%) group I patients had organic heart disease clinically: one had mitral valve disease and congestive heart failure (Case no. 7) and the other had aortic regurgitation and congestive heart failure (Case no. 9). The cause of death of group II patients was more varied (Table I): five from surgical complications (two hypophysectomy, two thyroidectomy, and one vocal cord polypectomy), three from cardiac failure, two from stroke, two from pulmonary emboli, one each from pyelonephritis, hydrocephalus, glioblastoma, and carcinoma of the lung. Although cardiac failure was the cause of death of only three of the 16 group II patients, seven other patients (a total of 10 or 37% of the total series of 27) had clinical evidence of congestive heart failure (Table I).

Organ weights. Compared with the expected organ weights according to the individual's body weight and body height,[3] the vast majority of both group I and group II patients had splanchnomegaly, including increased heart size: hepatomegaly 93%, splenomegaly 93%, renomegaly 81%, and cardiomegaly 81%. Only nine patients (33%) in the entire series had heart weights exceeding 500 g, all but one in group II (Table I). The largest heart in the series, 1,300 g, was 3.7 times the expected weight (Fig. 1). The increase in heart size appeared to be related to the duration of the disease (Fig. 2) and unrelated to the presence of hypertension or coronary artery disease. The proportions of patients with heart weights greater than the expected weights in group I and group II were 63.6% (seven of 11) and 93.8% (15 of 16), respectively. The difference was statistically significant ($p < 0.01$) according to the rank sum test. Cardiomegaly was disproportionate to hepatomegaly, splenomegaly, and renomegaly in 33%, 26%, and 30%, respectively (Figs. 3, 4, and 5). None of the hearts showed asymmetric septal hypertrophy.

Cardiac abnormalities. Clinical hypertension, defined as blood pressure recordings of 160/95 mm Hg or higher, was present in three (27%) of group I and nine (56%) of group II patients (Table I). Eleven of the 12 (91%) hypertensive patients had cardiomegaly. However, cardiomegaly was also common among the nonhypertensive acromegaly patients, being present in 73% (11 of 15) of cases. Four of the group I and none of the group II patients were diabetic. Significant coronary artery disease was present in three of 27 cases



Fig 1 A normal si ed 3,0 g heart *(on the left)* is dwarfed by the giant 1 300 g acromegalic heart *(on the right)*

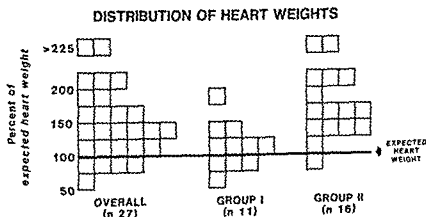


Fig 2 Histograms showing distribution of heart weight in acromegalic patients Expected heart weight according patient s body weight and body length is expressed as 100 percent Group I patients died within 10 year of lini al onset of acromegaly and group II patients died 10 or more years after the onset of acromegaly

(11(the ages of these three patients were 57 73 and 81 yea Gro s evidence of old myocardial infarction was found in four of 27 cases (15%) ag in each of these four patients was 57 years old or older Significant atherosclerosis of the abdominal a t t was f und in s of 27 cases (21%) five of the e i pat e s were 7 years old or older Aortic and mitral valvular heart disease was present in e t 27 cases (19%) two had aortic regurgitation tw had mitral stenosis and regurgitation (n n historically or morphologically rheumatic i fu tic in origin) and one had calcific aortic stenosis and regurgitation secondary to old h d t bacterial endocarditis

Review of m r h topathology generally showed varying d of myocardial hypertrophy and intersti l fibro s (Fig 6) Myocardial hypertrophy was present to some extent in 25 (93%) of 27 cases and involved the myocardium of both ventricles Focal myocardial fiber disarray (Fig 7) was observed in five cases (19%) Interstitial fibrosis was seen in 23 (85%) of 27 cases almost invariably accompanying myocardial hypertrophy Other histologic findings which appeared frequently were interstitial lymphomononuclear infiltrate and small vessel disease The myocardium in 16 of 27 cases (59%) showed a continuum of changes from mild nonspecific interstitial cellular infiltration to true myocarditis Myocarditis which may be focal or diffuse (Fig 8) was observed in seven hearts (26%) Six of 27 patients (22%) had significant wall thickening of the small intramural branches of the coronary arteries unrelated to myocardial scar tissue (Fig 9) Four

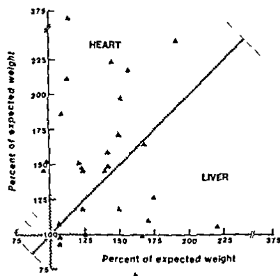


Fig 3 Comparison of the corresponding actual heart weight *(ordinate)* and actual liver weight *(ab ci a)* in acromegalic patients Expected organ weight according to patient s body weight and body height is expressed as 100 percent *The shaded area* represents ±25% of the expected (100%) organ weights *Points outside the shaded area* are regarded as disproportionate organomegaly heart to the left liver to the right of the diagonal solid line

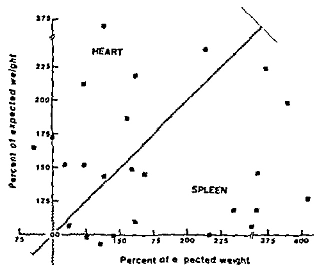


Fig 4 Comparison of the corresponding actual heart weight *(rdinate)* and actual pleen weight *(ab ci sa)* in acromegalic patients Expected organ weight according to patient s body wei ht and body height i expressed as 100 percent *The haded area* represents ±25% of the expected (100%) organ wei hts *P int ut i le the shade l area* are regarded as disproportionate organomegaly heart to the left pleen to the ri ht of the diagonal solid line

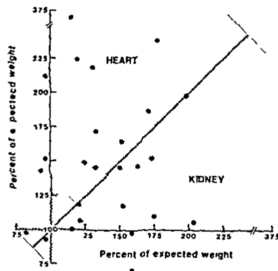


Fig 5 Comparison of the corresponding actual heart weight *(ordinate)* and actual kidneys weight *(ab ci a)* in acromegalic patients Expected organ weight according to patient s body weight and body height is expressed as 100 percent *The haded area* represents ±25% of the expected (100%) organ weights *Points outside the shaded area* are regarded as disproportionate organomegaly heart to the left kidneys to the right of the diagonal solid line

of the six patients who had small vessel disease of the heart were clinically hypertensive and one of the four also had diabetes mellitus The prevalence of the various pathologic changes of the heart in group I and group II patients are compared in Table II

An *additional autopsy finding* that occurred commonly was thyroid enlargement Only five of the 23 thyroids examined at autopsy were normal the remaining 18 (78%) were adenomatous (15 cases) or showed Hashimoto thyroiditis (three cases) It was noted that four of the 27 patients in this series had undergone thyroidectomy for hyperthyroidism

Discussion

Cardiac failure as a major cause of morbidity and mortality in acromegaly has been repeatedly emphasized in the past However most of the previously published studies of cardiovascular disorders in acromegaly are either purely clinical ly oriented or have included only a small number of autopsied patients There are also reports of large series that do not deal with cardiac findings in any detail The results of a recent prospective study of 57 patients by McGuffin and associates are at variance with many of the conclusions of the earlier studies notably the lack of correlation between hypertension cardiac disease and the growth hormone concentration in acromegaly Unfortunately only eight autopsied

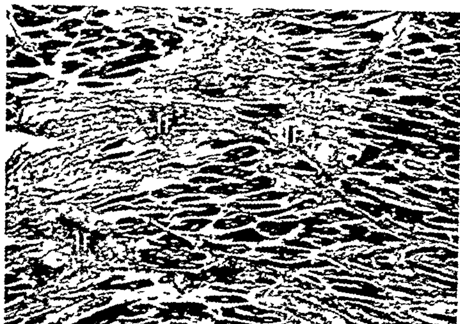


Fig 6 Typical histologic appearance of acromegalic heart showing interstitial fibrosis *(IF)* and hypertrophied myocardial fibers (Mallory Heidenhain stain original magnification ×1?0)



Fig 7 H [illegible] appearance of focal myocardial fiber disarray in acromegalic heart (Hematoxylin-eosin original [illegible])

cases were [illegible] in the report by McGuffin and [illegible]

Autopsy Series of Acromegaly Acromegaly is sufficiently [illegible] that the number of autopsy cases fr[illegible] single institution is necessarily limited In [illegible] survey of case records of acromegaly [illegible] different medical centers Wright and co-workers were able to identify a total of 194 cas[illegible] which there were 55 deaths but the postmortem reports were available [illegible] only 26 patients The 27 patients included in o[illegible] series were selected (on the basis of availability [illegible] tissue specimens for review) from a total of 4[illegible] autopsy cases in the Mayo autopsy record [illegible] 1919 to 78 In this 60 year period the to[illegible] number of autopsies performed at Mayo wa[illegible] 45 767 representing an autopsy incidence [illegible] acromegaly of 1 in 1 116



Fig 8 A Histologic appearance of myocarditis in acromegalic heart B The boxed area in A is seen at higher magnification showing individual myocyte necrosis and lymphomononuclear cell infiltrate (Hematoxylin-eosin A original magnification ×48 B original magnification ×300)

Review of our autopsy cases of acromegaly bears many disadvantages that are inherent to all retrospective studies but the potential benefits of understanding the pathogenesis of a disease process with the aid of detailed postmortem findings should be equally obvious Because all but four deaths in our series occurred before 1960 we lack data to comment on the significance of growth hormone concentration in relation to cardiovascular disorders of acromegaly This aspect has been fully discussed by McGuffin and associates The separation of our 27 autopsy cases into two groups though arbitrary (based on the known duration of acromegaly from diagnosis to death) makes interesting comparison with reference to the mortality cause of death and cardiac abnormalities (Table II)

Mortality and cause of death Patients with acromegaly are known to have a reduced life expectancy In the collective series of 194 cases reviewed by Wright and colleagues[11] 26% of deaths occurred before the age of 50 years and 64% by the age of 60 years Even higher figures were noted in an earlier study of 100 cases by

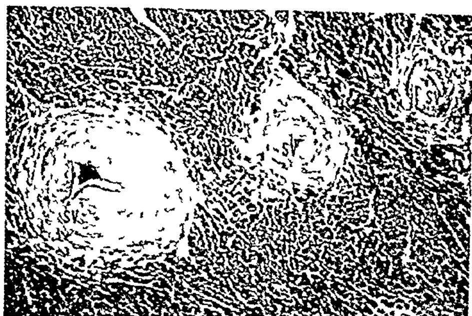


Fig 9 Histologic appearance of proliferative wall thickening of small intramural vessels (SV) in acromegalic heart (Hematoxylin eosin original magnification ×49)

Table II Cardiac pathology in acromegaly (autopsy series)

Group	Group I (n = 11)	Group II (n = 16)	Total (n = 27)
Sex ratio (M/F)	3/8	13/3	16/11
Mean age (yr) at death	39.5	57.9	50
Hypertension (≥ 160/95 mm Hg)	3 (27%)	9 (56%)	12 (44%)
Diabetes mellitus	4 (36%)	0	4 (15%)
Clinical heart failure	2 (18%)	8 (50%)	10 (3[illegible]%)
Cardiomegaly	7 (64%)	15 (94%)	22 (81%)
mean heart weight (g)	349	618	496
Coronary artery disease	0	3 (19%)	3 (11%)
Aortic atherosclerosis	0	6 (38%)	6 (22%)
Valvular heart disease	2 (18%)	3 (19%)	5 (19%)
Myocardial hypertrophy	10 (91%)	15 (94%)	25 (93%)
Interstitial fibrosis	8 (73%)	15 (94%)	23 (85%)
Cell infiltrate or myocarditis	5 (45%)	11 (69%)	16 (59%)
Small vessel disease	2 (18%)	4 (25%)	6 (22%)

[illegible] died [illegible] than 10 years of diagnosis of acromegaly Group II patients died more than 10 years after diagnosis of acromegaly
[illegible] expected weight by body weight or body length only [illegible] (36%) of [illegible] cardiomegaly cases were recognized clinically
[illegible] arteries with ≥ 75% cross sectional luminal narrowing
Abd[illegible] with ~ 50% surface area involvement by atherosclerosis
[illegible] the [illegible] with histological myocardial hypertrophy were within the normal range (i.e. no cardiomegaly)

Evans and co-workers who reported 50% of deaths before the age of 50 years and 89% by the age of 60 years. There was a heavy bias of surgical deaths in our group I patients nine of the 11 patients died before 1940 in the pre antibiotic era also at the time of the more hazardous transfrontal craniotomy for resection of pituitary tumors All seven (2[illegible] of the series) cardiovascular deaths (three cardiac failure two stroke and two pulmonary embolism) occurred in group I[illegible] patients in whom acromegaly was diagnosed fo[illegible] 11 to 39 years A greater prevalence of cardiovascular disorders among patients who had the[illegible] acromegaly longer was also noted in the prospec[illegible]tive series reported by McGuffin and asso[illegible]ciates

As has already been noted by Wright and colleagues the particular speciality of the ho[illegible]

tal may in part determine the observed causes of death in acromegaly Of the two older studies diabetic coma was the most common cause of death in a report published in 1927[4] and intracranial extension of the pituitary tumor was the commonest cause of death in another report published in 1964[7] In the survey conducted by Wright and co workers[13] increased mortality was found to be associated with hypertension and clinical diabetes but not with chemical diabetes The 26% incidence of deaths from cardiovascular disorders in our series was in close agreement with the 24% reported by Wright and colleagues[13]

Pathogenesis of cardiomegaly Organomegaly including cardiac enlargement has been so consistently identified with acromegaly that Levene and Miller[30] considered it worthwhile to report a case because the heart was normal in size Although the literature is replete with reports of acromegalic hearts in excess of 1 000 grams[4, 5, 7, 8] it is still more common to find acromegalic hearts weighing several hundred grams less than the kilogram range The mean heart weight was 486 grams in our series of 27 patients but a trend toward progressive cardiac enlargement with longer duration of acromegaly was evident The mean heart weight of our group I patients (acromegaly less than 10 years) was 348 grams whereas the mean heart weight of our group II patients (acromegaly more than 10 years) is 618 grams Of the 22 patients in whom cardiomegaly was found at autopsy only seven (36%) were recognized to have roentgenologic evidence of cardiac enlargement clinically

Disproportionate cardiomegaly (cardiac enlargement proportionately greater than enlargement of other visceral organs) has often been cited[11, 9] as a uniform finding in acromegaly This notion was unsupported by our autopsy data when cardiomegaly was compared with the enlargement of the liver spleen and kidneys in the same patient (Figs 3 4 and 5)

Premature or accelerated atherosclerosis as a cause for the cardiac hypertrophy in acromegaly was first suggested by Huchard in 1895 and an increased incidence of significant coronary and aortic atherosclerosis in acromegalic patients has been repeatedly cited since then[3] This was not substantiated by autopsy data since only 11% of cases had significant coronary artery disease and 22% of cases had significant aortic atherosclerosis (Table II) all signs were found in patients at an age when more advanced atherosclerosis would be expected normally

Valvular heart disease in association with acromegaly was seldom discussed in the past Courville and Mason[3] cited no data but stated that cardiac disease in patients with acromegaly was probably due to some etiologic factors other than valvular disease Indeed valvular disease was not uncommon (19%) in our patients and appeared to contribute little to cardiac hypertrophy in acromegaly

The importance of hypertension in cardiomegaly is highly contentious Reports of the incidence of high blood pressure in acromegaly range from 8 to 57%[7, 1, 16] The over all incidence of hypertension was 44% in our series it occurred twice as commonly in group II as in group I patients (Table II) Some authors postulate an important causal relationship between hypertension and cardiac enlargement in acromegaly[9, 1] but others disagree[1, 31] Although five of the seven largest hearts in our series were found in hypertensive subjects 11 (73%) of the 15 nonhypertensive patients also had cardiomegaly (Table I) Typically the hypertension was mild uncomplicated and responsive to drugs as previously noted by McGuffin and co workers[1]

Similarly it seemed unlikely that *diabetes* was a major etiologic factor of cardiomegaly in acromegaly only four (15%) of our 27 autopsied patients were diabetic In reviewing Harvey Cushing s patients Coggeshall and Root[6] found 26 (17%) *diabetes in 153 cases of acromegaly* The average interval between the onset of acromegaly and diabetes was 9 2 years According to the authors the clinical character of the diabetes associated with acromegaly did not show any greater variation in severity resistance to insulin and life expectancy than was seen in a large group of diabetic subjects without acromegaly

The direct effects of growth hormone on heart size remains an unsettled issue DeGrandpre and Raab[3] showed that repeated doses of growth hormone in the presence of a normal work load caused cardiac hypertrophy in rats Some authors feel this also applies to human hearts while other investigators deny it[14, 19, 1] According to McGuffin and colleagues[9] hypertension was the only abnormality that correlated with the plasma growth hormone concentration but a marked

reduction in plasma growth hormone concentration although not usually normal, did not *influence the hypertension*

Some authors[5,13,17,0] have suggested the possibility of a specific entity *acromegalic cardiomyopathy,* in which cardiomegaly is present in the absence of hypertension atherosclerosis, or severe valvular disease Indeed 33% (nine of 27) of cases in our series fell within this category (Table I) This possibility merits further consideration though the currently available evidence does not fully support it Two recently reported clinical studies[4] have shown that most acromegalic hearts function normally even when their mass is considerably enlarged and subclinical cardiac dysfunction is uncommon among asymptomatic patients with acromegaly However in an earlier study Jonas and co workers[9] reported a high incidence of subclinical cardiac muscle disease in 10 acromegalic patients on the basis of abnormal systolic time intervals

Another possibility that pituitary products other than growth hormone may be responsible for the unexplained cardiomegaly in acromegaly also warrants serious consideration Curtarelli and Ferrari[11] have recently reported an interesting case of massive cardiomegaly with heart failure in a 42 year old hyperprolactinemic woman in whom a pituitary tumor had been treated by radiotherapy five years previously Since prolactin is known to exert metabolic *growth hormone like effects in animals and in* man the authors conjecture that prolactin hypersecretion might induce or maintain cardiac disease in patients with pituitary tumors In a preliminary survey of 35 hyperprolactinemic subjects Curtarelli and Ferrari[11] have found five with raised blood pressure and four two of whom were normotensive with cardiomegaly on chest roentgenographs

Histopathology of acromegalic hearts The occurrence of myocardial hypertrophy and interstitial fibrosis in acromegalic hearts is well known[7] The heart weight of three patients with myocardial hypertrophy were within the normal range Nonspecific lymphomononuclear cell infiltrate (nine of 27 cases or 33%) true *myocarditis (seven of 27 cases or 26%)* and small vessel disease (six of 27 cases or 22%) have rarely been recognized or described previously Small vessel disease and foci of mild cellular infiltrates in the interstitium have been seen occasionally in hypertrophied hearts from a variety of causes, including acromegaly, but their etiology is unclear Nor is the etiology of myocarditis in acromegaly known Morphologically, the myocarditis in acromegaly is reminiscent of myocardial lesions observed in experimental animals *after norepinephrine infusion[34,36] and in patients* with pheochromocytoma[37] It is speculated that the myocarditis in acromegaly might be causally related to the altered homeostasis of endogenous catecholamine secretion Of interest a recent report by Van Loon[3] has shown abnormal plasma catecholamine responses to the suppressive effects of bromocriptin (a dopaminergic agonist) and luteinizing hormone releasing hormone in acromegalics Whatever the mechanism might be in the development of myocardial lesions in acromegalics myocarditis is a possible contributing factor to cardiac failure in these patients though not necessarily the cause of cardiomegaly

Conclusions Cardiomegaly was common but not inevitable, in acromegaly, being present in 81% of our series of 27 autopsy cases The enlarged heart seldom exceeded 200% (i e twice) of the expected heart weight according to the patient's body weight and body height Contrary to the prevailing view, disproportionate cardiomegaly (in comparison with hepatomegaly splenomegaly, and renomegaly) was not a uniform *finding it occurred in one fourth* to one third of our cases Cardiomegaly appeared to be related to the duration of acromegaly, and was present in both hypertensive and nonhypertensive subjects Our data did not support another common belief that premature or accelerated atherosclerosis and diabetes were causally related to acromegaly and *cardiac failure in acromegaly* The possibility that a specific acromegalic cardiomyopathy may exist cannot be discounted by the currently available evidence The significance of small vessel disease and myocarditis in acromegaly has not been discussed in earlier pathologic studies of acromegaly and warrants further probing

Summary

The morphologic characteris ... pathogen
esis of cardiac enlargement in ... remain
poorly understood partly bec ... paucity
of detailed anatomic studies ... s per

out elsewhere rheumatic fever has a truly wide spectrum of presentation and based on our observations a condition called mild rheumatic fever may indeed exist In our series we found that about one-fourth of the patients with rheumatic heart disease had presented with one or several episodes of recurring and migrating polyarthralgia with associated low grade fever one week to several months before carditis was diagnosed It would thus seem that perhaps in areas of high incidence some patients develop mild attacks of rheumatic fever which go unrecognized and subsequently develop a recurrent attack which is often looked upon as the first attack And the reason for failure to diagnose the mild attack is a simple and absolute reliance on the Jones criteria

It is perhaps advisable that until further knowledge is gained regardin the possibility of such sequences of events particularly in areas of high incidence the clinician should watch for patients with arthralgia high ASO titer and elevated erythrocyte sedimentation rate Such instances would certainly deserve closer observation regarding future streptococcal throat infection and occasionally in the presence of strong family or sibling history of rheumatic fever one may justify prophylaxis for some time Most certainly the parents of such children deserve a thorough orientation with regard to rheumatic fever Due to the rarity and non pecificity of subcutaneous nodules and *erythema marginatum* their usefulness *in the diagnosis of rheumatic fever can be questioned*. Thus, in the future a modified approach to the long honored Jones criteria may be warranted

Iraj Aryanpur Kashani M D F.A C C
Division of Pediatric Cardiology T 008a
University of California San Diego
School of Medicine
La Jolla CA 92093

REFERENCES

1 DiSciascio G and Taranta A Rheumatic fever in children Am Heart J 99 635 1980
2 Dutz W Rossipal E Ghavami H et al Persistent cell mediated immunodeficiency following infantile stress during the first 6 months of life Eur J Pediatr 112 117 1976
3 Dutz W Kahout E Rossipal E and Vessal K Infantile stress immune modulation and disease pattern Pathol. Annu 77 415 1976
4 Aryanpur Kashani I Acute rheumatic fever A review of pathogenesis diagnosis and a modified approach to Jones criteria and management Paediatrician (In press)
5 Gharagozloo R Jamshidi M S and Ghadimi H Microbiological and epidemiological study of streptococcal sore throat at a children s clinic in a one year study Pahlavi Med J 7 334 19 6
6 Aryanpur K I Nazarian I and Siassi B Rheumatic heart disease in the developing countries *in* Heart disease in infants children and adolescents Moss AJ Adams F H and Emmanouilides G eds Baltimore 1977 The Williams & Wilkins Company p 547
7 Aryanpur Kashani I and Shakibi J G Unpublished data
8 Aryanpur I Paydar M Shakibi J G Siassi B and Yazdanzar A Regression of pulmonary hypertension after mitral valve surgery in children Op rative management of rheumatic mitral val e disease Chest 71 354 19
9 Aryanpur I K. Shakibi J G Yazadanyar A et al Closed versus open mitral commissurotomy in children with rheumatic mitral stenosis J Thorac Cardiovasc Surg 76 ? 3 19 8
10 Burch G E Giles T D and Colcolaugh H L Pathogenesis of rheumatic heart disease Critique and theory Am Heart J 80 556 1970

Reply

To The Editor

We wish to thank Dr Aryanpur who comes to America from the rheumatic fever front line of a (ever so painfully!) developing country for his flattering and thoughtful comments The possibility that malnutrition early in life predisposes to rheumatic fever is intriguing especially since experimental studies have shown that chronic moderate protein deficiency increases susceptibility to group A streptococcal infections in mice as one of us and El Sadr noted in an earlier review more slanted toward pathogenesis Dr Aryanpur s advice that the clinician watch for patients with arthralgia high ASO and elevated ESR is well taken and so is the option of prescribing prophylaxis in some cases that do not quite fulfill the Jones criteria with pedantic completeness After all the Jones criteria are a *guide* to the clinician not a clinician And who can draw the line between a mild arthritis and a severe athralgia with any certainty? As Daniel McCarty is fond of saying (only half in jest) an arthralgia is often an arthritis minus a good physical examination

Germano DiSciascio M D
University of Alabama Medical School
Birmingham Ala
Angelo Taranta M D
Cabrini Medical Center
Dept of Medicine
227 E Nineteenth St
New York N Y 10003
and New York Medical College
Valhalla N Y

REFERENCES

1 Cooper W C Good R A. et al Effects of protein insufficiency on immune responsiveness Am J Clin Nutr 27 647 1974
2 El Sadr W and Taranta A The spectrum and the specter of rheumatic fever in the 1980s Franklin E C editor New York 1979 American Elsevier Publishing Co Inc

Beta blockers and running

To the Editor

In a letter to the Journal, Doctor Adrian Williams relates his experience of jogging while being on therapy with 80 mg propranolol daily for mild hypertension (Am Heart J 98 542 1979) He states that before a marathon I allow myself the luxury of stopping my treatment this seems the equivalent of a 20 pound weight loss and my performance improves by at least 20 to 30 seconds per mile"

The experience of Doctor Williams is probably shared by a number of physically active men on beta blockers and it seems important to clarify to what extent such therapy affects the physical capacity We have recently completed a study

American Heart Journal

An international publication for the study of the circulation

George E Burch *Editor*
James A Cronvich *Assistant Editor*
Peter C Gazes *Assistant Editor*

International Editorial Board

Walter H Abelmann *Boston Mass*
William B Abrams, *West Point Pa*
David I Abramson *Oak Park Ill*
Raymond P Ahlquist *Augusta Ga*
James K Alexander *Houston Tex*
A C Arntzenius, *Leiden The Netherland*
John B Barlow *Johannesburg South Afr*
Giorgio Baroldi, *Milan Italy*
Henry W Blackburn, *Minneapolis Minn*
Thomas M Blake *Jackson Miss*
S Gilbert Blount Jr., *Denver Col*
Eugene Braunwald *Boston Mass*
Howard B Burchell *Minneapolis Minn*
Eugenu I Chazov *Moscow U S S R*
Henri Chevalier *Paris France*
Te-Chuan Chou *Cincinnati Ohio*
Ernest Craige *Chapel Hill N C*
Arthur C DeGraff *New York N Y*
H Denolin *Brussels Belgium*
James E Doherty *Little Rock Ark*
Jesse E Edwards, *St Paul Minn*
Robert H Eich *Syracuse N Y*
Mary Allen Engle *New York N Y*
Ali M Fakhro *Manama Bahrain*
M Irene Ferrer *New York N Y*
Nancy C Flowers *Louisville Ky*
Nicholas J Fortuin *Baltimore Md*
Martin J Frank, *Augusta Ga*
Edward D Freis *Washington D C*
Julian Frieden *New Rochelle N Y*
Meyer Friedman *San Francisco Cal*
Jacques Genest *Montreal Canada*
Allan V N Goodyer *New Haven Conn*
Mervyn S Gotsman *Jerusalem Israel*
Joseph C Greenfield Jr *Durham N C*
Robert L Grissom *Omaha Neb*
Dale Groom *Oklahoma City Okla*
Rolf M Gunnar *Chicago Ill*
Warren G Guntheroth *Seattle Wash*
E. William Hancock, *Stanford Cal*
Herbert N Hultgren *Palo Alto Cal*
Hisoe Ichikawa *Nara Japan*
Lewis F January *Iowa City Iowa*
James N Karnegis *Minneapolis Minn*
John A Kastor *Philadelphia Pa*
Nodar N Kipshidze *Tbilisi U S S R*
Henri E Kulbertus *Liège Belgium*
Richard Langendorf *Chicago Ill*
J n Lequime *Brussels Belgium*
Maurice Lev *Chicago Ill*
Harold D Levine *Boston Mass*
R I Linden *Leed England*
F Loogen *Dusseldorf Germany*
Hugh A McAllister Jr *Washington D C*
Dan G McNamara *Houston Tex*
George E Maha *West Point Pa*
Alberto Malliani, *Milan Italy*
Bill L Martz *Indianapolis Ind*
Rashid A Massumi *Tehran Iran*
Clifford V Nelson *Portland Maine*
Satoshi Ohta *Tokyo Japan*
Eckhardt G J Olsen *London England*
Morton Lee Pearce *Los Angeles Cal*
Alfred Pick, *Chicago Ill*
Hubert V Pipberger *Washington D C*
Walter H Pritchard *Cleveland Ohio*
Ray Pryor *Denver Colo*
William Roberts, *Bethesda Md*
Robert C Schlant *Atlanta Ga*
H A Snellen *Leiden The Netherlands*
Walter Somerville *London England*
John Thomas, *Nashville Tenn*
Nong Ting *Taipei Taiwan*
Hironori Toshima *Kyushu Japan*
Chen Lang Tung *Shanghai China*
William H Wehrmacher *Chicago Ill*
Hein J J Wellens, *Maastricht The Netherlands*
Alberto Zanchetti, *Milan Italy*
Douglas P Zipes *Indianapolis Ind*

VOLUME 100

JULY DECEMBER 1980

(Int J Sports Med in press) where the effects of 80 mg propranolol and 100 mg atenolol and placebo (double blind design) on the 2 000 m running time was measured in a group of healthy volunteers and related these results to muscle fiber composition As expected individuals with a high percentage of slow twitch fibers ran faster both times than those with a high percentage of fast twitch fibers However when on propranolol the performance was relatively more impaired in individuals with a high percentage of slow twitch fibers than in those with a high percentage of fast twitch fibers Individuals with a high percentage of slow twitch fibers took 20% to 30% longer to complete their 2 000 m running On atenolol 100 mg the same individuals needed less than 10% longer to complete the 2 000 m running Thus cardioselectivity (β selectivity) seems to be of importance to joggers

Hypertensive individuals previously accustomed to physical activity can expect a certain degree of deterioration of their performance capacity when treated with beta blockers It seems important that adequate information about these side effects of beta blockers is included in the over all information to hypertensive patients

However it also seems important to warn against unguided withdrawal of antihypertensive drug therapy

Lennart Kayser
Peter Kaiser
Jan Karlsson
Stephan Rossner
Depts of Clinical Physiology and Internal Medicine
and the Laboratory for Human Performance
Karolinska Hospital
104 01 Stockholm Sweden

Reply

To the Editor

It is interesting to have the data of Dr Kayser and his colleagues to support my anecdotal experience with beta blockers and exercise The 20% to 30% slowing they noted in the 2 000 m time of individuals with a high percentage of slow twitch fibers (presumably those best equipped for running long distances) correlates well with this I am of course intrigued to think that cardioselective blockade might impede my training less but then the value of such "loaded" training would then be reduced

Adrian J Williams MB MRCP (Lond) Co Director
Pulmonary Function Laboratory
VA Wadsworth Medical Center
Wilshire and Sawtelle Blvds
Los Angeles Calif 90073
Asst Professor of Medicine
University of California Los Angeles

Lo—the poor Eskimo!

To the Editor

Dr Oster's Edit[illegible] [illegible] ity in a Committee Report on Diet and Coronary Heart [illegible] (AMERICAN HEART JOURNAL April 19[illegible] [illegible] attack the suggestion of the Nutrition Comm[illegible] [illegible] an Heart Association that a diet high in sat[illegible] [illegible] cholesterol is an important factor for a high incidence of coronary heart disease Dr Oster argues that to establish a causal relationship it must be shown that all population groups with a high saturated fat and cholesterol intake also exhibit a high incidence of atherosclerosis This is decidedly not the case with the French the Eskimos and the Masai, all populations *consuming diets high in saturated fats.*

The Eskimos are probably the most frequently quoted, or rather—as factual research in contrast to popular assumption has shown—misquoted example used *ad nauseam* in this controversy Most researchers found that Eskimo groups living a relatively traditional life style consumed despite their predominantly carnivore diet not more but substantially less fat than other North Americans Furthermore the fats they consumed although derived from animals were *not* highly saturated as presumed by Oster and others In fact, a much higher content of long chain polyunsaturated fatty acids than prevailing in North American diets was found in diets of Greenland Alaskan and Canadian Eskimos. Platelet lipid analysis in Greenland Eskimos reflected their high consumption of omega 3 polyunsaturated fatty acids and this results in a significantly longer bleeding time due to a reduction in platelet aggregation

These recent biochemical and physiological findings may explain earlier epidemiological observations that Eskimos were relatively free of thrombotic cardiovascular diseases but suffered from increased bleeding tendencies with undue frequency of severe postpartum hemorrhage and Sheehan's syndrome The degree of deviation from modern North American norms or the inversely related thrombotic and bleeding tendencies in various Eskimo population groups shows clear trends in geographical distribution and changes with time best explained by changes in their diet

Eskimos do therefore provide a good example *for and not against* the validity of the fourth report of the American Heart Association Committee on Nutrition and similar recommendations issued in recent years in various countries.

I hope that drawing attention to these facts will help to relieve the Eskimos from being used as *false witnesses for the* fat lobby a practice entrenched by repetition of popular myths never supported by factual research Indeed, their example provides valid ammunition *for the side advocating* dietary intervention I suspect that *the other two population* groups used in your editorial argument against the recommendations of the Nutrition Committee—namely the Masai and the French—are also not very suitable examples The Masai are subjected to frequent periods of famine and regularly have to walk long distances as nomadic cattle herders [illegible] French men drink fair amounts of wine Famine physical exertion and wine drinking all tend to elevate high density lipoproteins which may counteract the effect of low and very low density lipids and cholesterol There may be other complicating factors evident to observers more familiar with local conditions in France and East Africa than I am

O Schaefer MD FRCP(C)
Northern Medical Research Unit
Medical Services
N H W Reg[illegible]
c/o Charles Camsell Hospital
12815 115 Avenue
Edmonton Alberta
T5M 3A4 Canada

VOLUME 100
COPYRIGHT © 1980 BY
THE C. V. MOSBY COMPANY
All rights reserved

Printed in the United States of America

REFERENCES

1. Heller C A and Scott E M The Alaska Dietary Survey 1956 61 Anchorage Alaska 1967 Publ Health Services, Publication No 999 AH 2
2. Uhl E (article written in 1955) cited by Bang H O Dyerberg J and Hjørne N The composition of food consumed by Greenland Eskimos Acta Med Scand 200 69 19 6
3. Schaefer O Medical observations and problems in the Canadian Arctic Can Med Assoc J 81 386 1959
4. Schaefer O When the Eskimo comes to town Nutrition Today 6 8 1971
5. Kemp W B The flow of energy in a hunting society Scientific American 225 10, 1971
6. Bang H O Dyerberg J and Hjørne N The composition of food consumed by Greenland Eskimos Acta Med Scand 200 69 1976
7. Wo C K W and Draper H H Vitamin E status of Alaskan Eskimos Am J Clin Nutr 28 808 1975
8. Hoppner K McLaughlan J M Shah B G Thompson J N Beare Rogers J Ellestad Sayed J and Schaefer O Nutrient levels of some foods of Eskimos from Arctic Bay N W T Canada J Am Dietetic Assoc 73 257 19 8
9. Dyerberg J and Bang H O Haemostatic function and platelet polyunsaturated fatty acids in Eskimos Lancet 2 433 1979
10. Lederman J M, Wallace A C and Hildes J A Arteriosclerosis and neoplasms in Canadian Eskimo in Schock N W ed Proceedings of the Fifth Congress of the International Association of Gerontology New York 1962 Columbia University Press pp 201 207
11. Mann G V Schaffer R D Anderson R S et al Cardiovascular disease in the Masai J Athero cler Res 4 289 1964
12. Bliss K Ho K J Mikkelson B Lewis L and Taylor C B Some unique biologic characteristics of the Masai of East Africa N Engl J Med 284 694 1971
13. Keys A and Keys M How to eat well and stay well the Mediterranean way Garden City N Y 1975 Doubleday & Co Inc Appendix p 467 Table 2

Reply

To the Editor

It would indeed be presumptuous of me to enter into an argument with Dr Schaefer about the diet of the Eskimos I accept his expertise on this subject However in its imbalance the Eskimo diet does not approximate the American Heart Association Committee on Nutrition s suggested dietary proportions nor do the Eskimos have high serum cholesterol values. Eskimo summer food was found to consist of 3 protein 21% fats and 46% carbohydrates With this high protein consumption it is understandable how the name Eskimo or eater of flesh " was derived Eskimos prefer to be called Inuit (man)

The low heart attack rate of the Eskimos is ascribed to their intake of eicosapentaenoic acid (EPA) which might be partially substituted for arachidonic acid thereby reducing thrombogenesis However the diet which causes bleeding tendencies in the flesh-eating Inuit seems to have no influence on serum cholesterol. I do not think Dr Schaefer would suggest such an unbalanced diet for the North American population at large

It is disconcerting to me that Dr Schaefer falls into the common trap of alibiing commonly known findings in order to prop up the faltering diet heart cholesterol hypothesis I have studied the nutrition of the Masai and published my findings Their diet includes 60% saturated fats from curdled milk It is ludicrous to equate their lack of coronary heart disease with the walking of long distances and frequent periods of famine The lumber workers of East Finland an agrarian population expend much more of their caloric energy in pursuing their livelihood than do nomadic cattle herders They live in a lower stress situation than an urban population and still have the highest coronary heart disease rate in the world I hope that Dr Schaefer is not serious when he accepts the wine drinking habits of French men as the reason for their experiencing less coronary heart disease than similar American men with the identical risk factor constellation despite the documented high saturated fat intake of the French This naivete of wishing away findings contrary to one s favorite idea is shared by Stamler who blames the differences in coronary heart disease incidence between European and American men on the European food deprivation of World War II another alibi Even the mentors of the Framingham Study have changed their opinion about serum cholesterol "The previous position that virtually all of the lipid information pertaining to coronary heart disease resided in the serum total cholesterol must be (accordingly) modified

Self styled and chest thumping experts transpose a paucity of nutritional knowledge into an abundance of diverse and questionable advice on altering nutrition and the food supply system of the nation A brouhaha was created in May 1980 by the recommendation on fats and cholesterol in the diet by the Food and Nutrition Board of the National Academy of Sciences National Research Council The Board s action was consistent with its recommendations of 1972 However slanted nutrition research in the political arena has fostered dissension and varied and unsubstantiated recommendations Examples are (1) U S Senate Select Committee on Nutrition and Human Needs *Dietary Goals for the United States* (2) U S Department of Agriculture and the U S Department of Health Education and Welfare *Nutrition and Your Health Dietary Guidelines for Americans* and (3) the Surgeon General s report on health promotion and disease prevention *Healthy People* Each differs in its stance on cholesterol and fats, and all are out on a limb Proponents of dietary changes have not come to a meeting of the mind and stray in different directions thereby confusing the American consumer The dissonance of recommendations in the ranks of the AHA s Committee on Nutrition which was the theme of my Editorial has spread and is now to be found in most nutrition scenarios of politically inspired organization

Cuius pecunia eius dieta (Whose money his diet)

Kurt A Oster MD
881 Lafayette Blvd
Bridgeport Conn 06604

REFERENCES

1. Bang H O Dyerberg J and Hjørne N Investigation of blood lipid and composition of food of Greenland Eskimos (Abstr) Nutrition Today 9 1 1974
Dyerberg J and Bang H O Hemostatic function and platelet polyunsaturated fatty acids in Eskimos Lancet 2 433 1979
3. Oster K A Plasmalogen diseases and the rarity of

Author index*

*July pp 1 138 August pp 139 274 September pp 275-416 October pp 417 594 November pp 595 772 December Part 1 pp 773 976 December Part 2 pp 977 1090

atherosclerosis in the Masai *in* Myocardiology in Africa Nairobi Africa 1974 E A Community (CES) Chap 5 1 209
4 Stamler J Population studies *in* Nutrition Lipids and Coronary Heart Disease Levy R I., Rifkind B M., Dennis B H., and Ernst N D., eds New York 1979 Raven Press p 61
5 Kannel, W B Castelli W P and Gordon T Cholesterol in the prediction of atherosclerotic disease new perspectives based on the Framingham Study Ann Intern Med 90 85 1979
6 Blackburn H Diet and mass hyperlipidemia public health considerations, *in* Diet Related to Killer Diseases VI Appendix Washington D C July 26 1977 U S Government Printing Office pp 101 140
7 O ter K A. Dietary goals—dreams and reality Conn Med 42 705 1978

Rupture of myocardium and mitral valve replacement

To the Editor

In their article in the January 1980 issue of the AMERICAN HEART JOURNAL Cobbs and associates have presented eight cases of rupture of the myocardium as a result of mitral valve replacement involving severance of the chordae tendineae

We have been mea uring the fiberpath angles of the myocardium in humans and other mammals for some years now and have shown conclusively that the angle change transition from epi to endocardium in the normal heart is smooth and predictable The fiberpaths obey a theorem of Clairaut which states that r cos α = a constant This translates into radius times the cosine of the angle tangential to the epicardium is a constant

The fiberpath angles at epicardium (and at endocardium) are dependent upon the shape and size of the heart and the thickness of the myocardium If the wall is thick—i.e the ratio of the in ide diameter to the outside diameter (r /r₀) in the contracted state is mall the angles are likely to be steeper at epicardium (~ −80 degrees ± 10 degrees) and at endocardium (~60 degrees ± 10 degrees) than if the ratio is large (α at epicardium ~ −60 degrees ± 10 degrees at endocardium ~40 degrees ± 15 degrees, relative to the longitudinal axis running through the left aortic valve commissure and the apex of the left ventricle) At least, that is what we have found If the epicardial fiberpaths can be seen and if the wall thickness is known a very rough estimation of the endocardial fiberpath angles can be made In fact if the epicardial angle is known and the r /r ratio is known the angles can be estimated again very roughly through the whole thickness of the myocardium by drawing a strai ht curve from say −70 degrees to 50 degrees If we divide the wall thickness into quantiles, the epicardial quantile is in t alance with the endocardial quantile in accordan e with the Clairaut theorem The quantile next inside epicardium is in balan e with the quantile next in ide endocardium and so on W h wn th perimentally It is obvious th refore that s ra f th hordae tendi neae in mitral val e repl en lea th n rdium just basal to the papill m sc r tt n at in lan e with the epicardial fiberpath at th tud h m v fiber because it is a branched structure f m king a dju tment to the pred minant fiber th th w thin the sibility of its branches If the a n nt rupture must

(As ass med zero)

and does occur Fig 3 (Case No 2) of Cobbs and associates article shows dramatically that an attempt at readjustment was made It failed Balance could not be restored The figure also shows the transition from the midwall cross-cut fibers on the right, via those cut at intermediate oblique angles, to those which the authors call plunge fibers" that we suspect are fiberpaths that had attempted to restore Clairaut balance but failed.

Leaving the chordae tendineae attached to the posterior leaflet intact preserved the Clairaut balance Ideally all chordae should be left intact but if severance is unavoidable perhaps collagen sutures longitudinally oriented from the free end of the papillary muscle would take up the load longitudinally

M Alison Ross MA
Daniel D Streeter Jr PhD
Division of Cardiology
The Children s Orthopedic Hospital and Medical Center
P O Box C-5371
Seattle Wash. 98105

REFERENCES

1 Cobbs B W Jr Hatcher C R Jr and Craver J M Transverse midventricular disruption after mitral valve replacement AM HEART J 99 33 1980
2 Streeter D D Jr Gross morphology and fiber geometry of the heart *in* Berne R M and Sperelakis N eds The heart Handbook of physiology circulation nd ed Bethesda Md American Physiological Society pp 61 112
3 Struik D J Lectures on Classic Differential Geometry 2nd ed Reading Mass., 1961 Addison Wesley p 1

Reply

To the Editor

I thank Ms Ross and Dr Streeter for their thoughtful letter and regret not having been previously familiar with their detailed anatomical work which offers elegant theoretical ground for expecting the complication we described As they imply the structure we call the mitral loop is merely part of a complex system of epicardial to endocardial fiber paths It is a pleasure to learn that our concept of a dynamic balance of tension between epicardial and endocardial members of the loop may have mathematical validity We believe that mid ventricular disruption has been around for a long time often in latent or only partly expressed form But the advent of cardioplegia and perhaps trut trauma from the new hypothermia theses have set the stage for a fuller realization of the ul ma e pathology

B Woodfin Cobbs Jr MD
Section of Internal Medicine
Division of Cardiology
Emory University Clinic
1365 Clifton Road NE
Atlanta Ga 3

Cyclophosphamide cardiomyopathy

To the Editor

The Annotation on anthracycline cardiotoxicity by Henderson and Frei very nicely summarizes both acute and chr

D

E

F

G

toxicities associated with the use of these agents The incidence of these phenomena is likely to increase with the recent approval of daunorubicin for treatment of adult nonlymphocytic leukemia by the FDA so their information is timely

In their report however Henderson and Frei state that cyclophosphamide (CTX) when used in large single doses has caused acute mild pericarditis The fact of the matter is that CTX in large doses (144 to 2 0 mg /kg) used prior to bone marrow transplantation has caused death from severe refractory myocardial failure Signs of CTX cardiomyopathy include loss of R waves and ST T wave changes on the ECG However interpretation of these findings is difficult because they are nonspecific and frequently transient The incidence of ECG changes at doses of 170 mg /kg of CTX appears to be approximately 90% Also elevation in serum myocardial enzymes (CK, SGOT and LDH) has been observed at approximately a 40% frequency with the same dose Overt congestive heart failure did not occur at this dose

When compared with anthracycline cardiomyopathy CTX s effects appear to be different CTX cardiomyopathy has an acute onset with death occurring from intractable heart failure in reported cases within 15 days of the initial dose The effects are dose-related but do not appear to be the cumulative result of long term drug administration Cardiac morphology at autopsy is characterized as hemorrhagic myocardial necrosis which may be focal with fibrin microthrombi in capillaries and interstitial fibrin deposition An exudative nonmalignant pericardial effusion is usually present in addition to pulmonary edema and ventricular hypertrophy A proposed mechanism of CTX cardiotoxicity is direct endothelial damage leading to extravasation of blood containing high concentrations of drug which subsequently produces myocardial cell damage fibrin precipitation and focal hemorrhage with development of refractory congestive heart failure Unlike anthracycline cardiotoxicity no risk factors for CTX cardiomyopathy have yet been identified

As more is learned about marrow transplantation and the aggressive nature of conditioning regimens using high doses of chemotherapeutic agents increases the frequency of many untoward effects including cardiotoxicity is also likely to increase

Raymond W Roberts Pharm.D
Director of Pharmacy Services
Riverside Hospital
2033 Riverside Ave
Jacksonville FL 32204

REFERENCES

1. Henderson I C and Frei E Adriamycin cardiotoxicity (Letter to Editor) AM HEART J 99 671 1980
2. Anonymous Daunorubicin (Cerubidine) Med Lett Drugs Ther 22 33 1980
3. Santos G W Sensenbrenner L L Burke P J Mullins G M Bias W B Tutschka P J and Slavin R E The use of cyclophosphamide for clinical marrow transplantation Transplant Proc 4 559 1972
4. Buckner C D Clift R A Fefer D D Funk D D Glucksberg H Ramsberg R E Storb R and Thomas E D Aplastic anemia treated with marrow transplantation Transplant Proc 5 913 1973
5. Buckner C D Rudolph R H Fefer A Clift R A Epstein R B, Funk D D Neiman P E Slichter S J Storb R and Thomas E D High dose cyclophosphamide therapy for malignant disease Cancer 29 357 197
6. Applebaum F R, Strauchen J A Graw R G Savage D D Kent K M Ferrans V J and Herzig G P Acute lethal carditis caused by high dose combination chemotherapy Lancet 1 58 1976
7. Gottdiener J S Applebaum F Deisseroth A B and Zeigler J L Cardiotoxicity associated with high dose cyclophosphamide (Abstract) Clin Res 26 5 A 1978
8. Mills B A and Roberts R W Cyclophosphamide induced cardiomyopathy Cancer 43 2-3 1979
9. Buja L M and Ferrans V J Myocardial injury produced by antineoplastic drugs Recent Adv Stud Cardiac Struct Metab 6 487 1975

Reply

To the Editor

We agree completely with the comment made by Dr Roberts in the above letter In fact the sentence which he quotes from our article represents a typographical error in the initial submitted manuscript which was not picked up in multiple proofreadings The correct statement as concerns Applebaum and associates in the quoted reference should have been that single doses have caused acute myocarditis instead of mild pericarditis We appreciate Dr Roberts bringing this point to the attention of readers because we too feel that it is an important point

I Craig Henderson M D
E Frei III M D
Harvard Medical School of Medicine
Sidney Farber Cancer Institute
44 Binney
Boston Mass 02115

REFERENCES

1. Applebaum F R Strauchen J A Graw R G Jr Savage D D Kent K M Ferrans V J and Herzig G P Acute lethal carditis caused by high dose combination chemotherapy A unique clinical and pathological entity Lancet 1 58 1976

Effects of antiarrhythmics in ischemic models

To the Editor

We read with interest Levites and Anderson s paper concerning the electrophysiological effects of disopyramine during myocardial ischemia They and several other authors have shown local anesthetic antiarrhythmics to possess degrees of selective electrical depression in ischemic models As postulated by Levites and Anderson nonuniform drug distribution within myocardial tissue may be an important explanation of selective depression of ischemic tissue by antiarrhythmic drugs We would like to offer a working model regarding altered antiarrhythmic availability to the ischemic myofibril

As a result of ischemia normal myocardial substrate utilization is transformed to anaerobic glycolysis with an ensuing intracellular acidosis The magnitude of the acidosis in the extracellular space exceeds that of extracellular fluid with intracellular pH dropping below 6 0 Recent information seems to show that local anesthetic antiarrhythmic actions are dependent upon an active ionized form and their ability to gain entrance to an intracellular site of action Because local anesthetics are weak bases and considering the intracellular acidosis present in the ischemic myocardium Kupersmith and colleagues theorized a higher degree of intracellular ioniza

H

I

J

Table I

Agent	Acid/base	pKa	% ionized at pH 7.4	% ionized at pH 6.0
Quinidine	Base	8.34	90	99
Procainamide	Base	9.24	98	99
Disopyramide	Base	8.36	90	99
Lidocaine	Base	7.86	73	99

tion of the antiarrhythmic Thus the availability of active cationic antiarrhythmic to an intracellular receptor site may improve

Table I shows the pKa and percent ionized at pH 7.40 (physiologic) and pH 6.0 (ischemic intracellular space) for several local anesthetic antiarrhythmics The percentage ionized of disopyramide increases to nearly 100% in an acid media Quinidine and procainamide show similar changes with lidocaine changing most in percent ionized from physiologic to acid pH In publications investigating these antiarrhythmics it appears that the *degree* of selectivity in ischemic tissue parallels the change in percent of drug ionized expected to be available in the intracellular space

Further studies similar to Levites and Anderson's are certainly warranted to elucidate effects of antiarrhythmics in ischemic model. We believe the physicochemical properties of specific local anesthetic antiarrhythmics remain the key to understanding the concept of selective depression of ischemic tissue

Jerry L Bauman Pharm D
Assistant Professor Pharmacy Practice
Robert A Curtis Pharm D
Assistant Professor Pharmacy Practice
University of Illinois at the Medical Center
College of Pharmacy
Chicago Ill 60612
Joel O Covinsky
Associate Professor of Clinical Pharmacy
University of Missouri Kansas City
Colleges of Medicine and Pharmacy
Kansas City Mo

REFERENCES

1 Levites R and Anderson G J Electrophysiological effects of disopyramide phosphate during experimental myocardial ischemia Am Heart J 98 339 1979
2 Honodeghem L M Effects of lidocaine phenytoin and quinidine on ischemic canine myocardium J Electrocardiol 9 203 1976
3 Hondeghem L M Grand A O and Jenson R A Antiarrhythmic drug action Selective depression of hypoxic cardiac cell Am Heart J 87 602 1974
4 El Sherif N et al Re-entrant ventricular arrhythmias in the late myocardial infarction period Mechanism of action of lidocaine Circulation 56 395 1977
5 Lazzara R et al Effects of lidocaine on hypoxic and ischemic cardiac cells Am J Cardiol 42 8?? 1978
6 Trump F B et al Studies on the subcellular pathophysiology of ischemia Circulation 53(Supp) 117 1976
7 Krug A Alteration in myocardial hydrogen ion concentration after temporary coronary occlusion A sign of irreversible cell damage Am J Cardiol 36 214 1975
8 Gebert G Benzing H and Strohm M Changes in the interstitial pH of dog myocardium in response to local ischemia hypoxia hyper and hypocapnia, measured continuously by means of glass microelectrodes, Pflugers Arch 329 72 1971
9 Gliklich J I and Hoffman B F Sites of action and active forms of lidocaine and some derivatives on cardiac Purkinje fibers Circ Res 43 638 1978
10 Kupersmith J Antman E M and Hoffman B F In vivo electrophysiological effects of lidocaine in canine acute myocardial infarction Circ Res 36 84 1975

Serum myoglobin as a sensitive index of myocardial infarction

To the Editor

We read with great interest the article of Tommaso Salzeider Arif and Klutz concerning CK and myoglobin in myocardial infarction We disagree however with their statement that myoglobin is an insensitive marker of myocardial necrosis in its early phase because of its lack of appearance in 50% of their patients having definite acute myocardial infarction

We have recently examined 15 patients with acute myocardial infarction seven with diaphragmatic infarction and eight with anteroseptal infarction In all patients frequent blood samples were drawn for determination of serum myoglobin total CK and CPK MB isoenzyme (? samples for each marker during 50 hours)

Total CK determination was performed according to the method of Rosalki The CK MB fraction was detected by electrophoresis on cellulose acetate plates For the measurement of CK MB a densitometric method was used by scanning the electrophoretic fraction of MB with the quick scan fluris The amount of CK MB was calculated as a percentage of the total CK activity Serum myoglobin levels were determined by radioimmunoassay using a kit from Nuclear Medical Systems Inc Newport Beach California

We found that significantly elevated serum myoglobin indicative of infarction was present 3 hours following the onset of chest pain in all patients examined and predated elevations of total CPK and CPK MB by 6 to ? hours Utilizing the sensitive radioimmunoassay for detection of myoglobin we found no evidence for the staccato phenomenon previously described

The interval during which the myoglobin assay remained elevated following infarction was found to be up to 50 hours (mean 3? hours) somewhat longer than previously described in the literature (24 hours) On comparing patients with diaphragmatic infarction (group A) to those with anteroseptal infarction (group B) we found significant differences in the myoglobin time curves a five hour plateau observed only in group B patients However the interval during which myoglobin was elevated was longer in group A patients by about 35 hours

A time sensitivity curve was drawn for myoglobin and CK MB which showed that serum myoglobin preceded CK MB for the 50% sensitivity time (by three hours) and for the 100% sensitivity time (by six hours) (Fig 1)

None of the patients serving as the control group had elevated CK MB total CK or serum myoglobin levels above normal

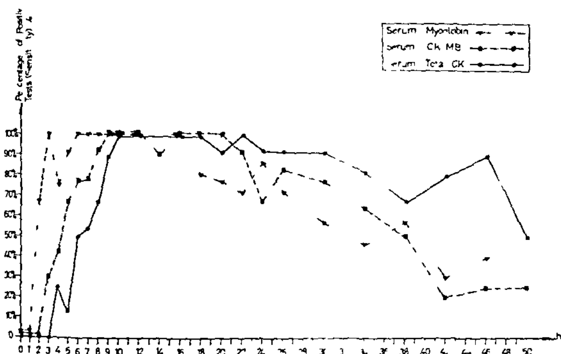


Fig 1 Time (hours) sensitivity curve of serum myoglobin, total CK and CK MB isoenzyme of patients examined.

values (for total CK 90 I U., for CK MB isoenzyme less than 4% of total CK, for myoglobin 85 ng/cc) It is apparent though that myoglobin is a very sensitive indicator of myocardial infarction and since it decreases to normal levels rather quickly it can serve as a valuable aid in the diagnosis of reinfarction and infarct extension CK MB is also a sensitive indicator of myocardial infarction and has the additional quality of high specificity Thus these assays combined will provide a most sensitive and specific early indicator of acute myocardial infarction

E Grenadier
S Keidar
A Palant
Department of Cardiology
Lady Davis Carmel Hospital
Haifa Israel

REFERENCES

1. Tommaso C L, Salzeider K., Arif M and Klutz W Serial myoglobin vs CPK analysis as an indicator of uncomplicated myocardial infarction size and its use in assessing early infarct extension AM HEART J 99 149 1980
2. Kagen L, Scheidt S and Butt A Serum myoglobin in myocardial infarction the staccato phenomenon Am J Med 62 86 1977
3. Marmor A, Alpan G Keidar S Grenadier E., and Palant, A The MB isoenzyme of CK as an indicator of severity of myocardial ischemia Lancet 2 812 1978
4. Varki, A. P., Roby D S., Watts, H and Zatuchni J Serum myoglobin in acute myocardial infarction A clinical study and review of the literature AM HEART J 96 680 1978

Reply

To the Editor

The work of Grenadier Keidar and Palant is appreciated Our evidence would tend to agree with theirs concerning the sensitivity of a myoglobin rise as an indicator of myocardial necrosis. In our patients reported all of whom were found to have enzyme evidence and ECG criteria consistent with transmural infarcts there was a detectable rise in serum myoglobin concentration. This suggests that at least in this small group of patients, a myoglobin rise is indeed sensitive for the presence of myocardial necrosis

This is consistent with the accumulated experience which has found a 75 to 100% rate of increased serum myoglobin in comparison with other indicators of myocardial necrosis.

Of interest is their finding of elevated serum myoglobin levels at only 1 5 hours following the onset of the clinical event Although it has been reported that myoglobin concentration will begin to rise within two hours after the ligation of a canine coronary artery previous work suggests this may not be the case in humans In our group there were four patients who did not have elevated myoblobin levels when sampled upon arrival in the emergency room. In our group sampling was done an average of 2.5 hours following the onset of symptoms, and the average time from symptoms to first detectable myoglobin elevation was almost four hours This yields a sensitivity of 50% as an early indication of myocardial infarction in patients who were selected because of ECG evidence of transmural infarctions This is in agreement with the data of Gilkeson and associates who found myoglobin elevation in only 40% of patients seen in an emergency room who subsequently had evidence of myocardial necrosis

This discrepancy may be due to the difficulty in timing of the onset of an out of hospital clinical event rather than the sensitivity of the assay which has been most reliable and quite accurate

The statement that use of early sampling is relatively insensitive is hence based on comparison to confirmatory ECG changes and was intended to discourage the use of myoglobin as an emergency room screening tool However I do concur with Grenadier and co workers assessment that serial myoglobin determinations may be potentially useful as a guide to determining episodes of reinfarctions or infarct extension in patients with acute infarction

Carl L Tommaso M D
Division of Cardiology
Department of Medicine
Northwestern Memorial Hospital
Northwestern University
2?0 East Superior St
Chicago Ill 60611

REFERENCES

1 Varki A. P Roby D S Watts H and Zatuchni J Serum myoglobin in acute myocardial infarction. A clinical study and review of the literature AM HEART J 96 680 1978
2 Willerson J T Poliner L Buja L M et al. Myoglobinemia as a clue to the presence of acute myocardial infarction (Abstr) Clin Res 24 422A 19 6
3 Gilkeson G Stone M J Waterman M et al. Detection of myoglobin by radioimmunoassay in human sera Its usefulness and limitations as an emergency room screening test for acute myocardial infarction AM HEART J 95 70 1978

R

S

Book reviews

Neural Mechanisms in Cardiac Arrhythmias Edited by Peter J Schwartz, Arthur M Brown Alberto Malliani and Alberto Zanchetti, New York 1978 Raven Press 460 pages Price $35 00

This publication contains reports presented in Florence during 19 8 on not only an important aspect of cardiology but on some much neglected aspects of cardiology The role of the central nervous system and the autonomic nervous system in the regulation of the central and peripheral circulation is clearly and succinctly reviewed by the many contributors to this publication The investigators in Milan Italy have been responsible in large part for the symposium Among the subjects discussed are arrhythmias, sudden death electrophysiology as influenced by the nervous system cardiac reflexes, baroreceptors and pharmacology The many papers are well illustrated and the references are carefully selected This is an excellent publication which certainly should interest all cardiologists and trainees in cardiology

British Medical Bulletin Smooth Muscle Edited by E Bulbring and T B Bolton London 19 9 The Medical Dept The British Council 107 pages Price $12 50

This is an excellent issue of the *Bulletin* The physiology and function of smooth muscle are clearly described A great deal of the discussions are devoted to vascular smooth muscle Physicians and certainly physiologists, who are concerned with vascul r phy iology will find it extremely profitable to tudy this i ue and even to own a copy for future reference The many contributors have done an outstanding job in summarizin the recent extensive advancements in knowledge of smooth muscle in this September 1979 issue of the *British Medical Bull in*

Advances in Card ovascular Physics Volume I Theoretical Foundations of Cardiovascular Processes Edited by D N Chista F Van Vollenhoven W J Yang and H Reul Basel Switz rlan l 19 9 S Karger AG 18 pages. Price $64 06

This is the first volume of *Advances in Cardiovascular Ph i* This volume should interest physicists bioengineers and phys olo i t involved in the biophysical interpretation of card v cular phenomena Among the subjects discussed are electrophysiology of the heart biomechanics of blood flow biotr n p rt mechani m and thermoregulation Clinicians will n t understand this series of publication but a perusal of th publ ation will clearly indicate the intricacies of h y nami phenomena which clinicians so casually take f r ted Physi i ts will find the publications to be ex r el luable but will quickly learn the intricacies and m i xities f biologic processes. This is a good publication th initiate a much needed a pect of cardiovascular con er n in research and the practice of medicine

Books received

Coronary Heart Surgery A Rehabilitat on Measure Edited by H Roskamm and M Schmiziger Seacaucus N J 19 9 Springer Verla New York Inc 394 pages Price $42 90

Sk n Deep: The Makings of a Plastic Surgeon By Donald T M n han M D nd Shirley Hartman Boston 19 9 Little Brown & Compar y 339 pages Price $10 00

Clin cal Card olc gy By Maurice Sokolow M D and Malcolm B McIlroy M D Los Altos Calif 19 9 Lange Medical Publishers, 718 pages

Primary Care Judgments of Nurses and Physicians Vol 4 Relia lity and Val dity Research Report By Frank E McLaughlin John W Carr and Kevin L Delucchi San Francisco 19 9 Veterans Administration Medical Center 70 pa es

Microcirculation—Volume I Edited by Gabor Kaley and Burton I Altura Baltimore 1979 University Park Press 528 pages. Price $44 50

Monographs on Atheroscle osis Part 9 Clin cal Methods in the Study of Cholesterol Metabolism Edited by David Kritche ky and O J Pollak written by H S Dodhi, B J Kudchodkar and D T Mason Basel 19 9 S Karger AG 16 pages Price $53 50

New Pathways in Laboratory Med cine Edited by S B Rasolki Bern Switzerland 19 8 Hans Huber Publishers, 142 pages

D agnosis and Therapy of Coronary Artery Disease Concepts and Controvers es Edited by Peter F Cohn M D Boston 19 9 Little Brown & Company 509 pages Price $32.50

Pla n Film Interpretat on in Congenital Heart Disease sec ond ed tion By Leonard E Swischuk M D Baltimore 19 9 The Williams & Wilkins Company 766 pages Price $28.50

International Symposium on Myocardial Hypertrophy

An International Symposium on Myocardial Hypertrophy ponsored by the American Section of the International Society for Heart Research will be held in Burlington Vermont on June 14 through 17 1981 For further information contact Dr Norman Alpert Professor of Physiology College of Medicine University of Vermont Burlington Vt 05401

Workshops of International Society for Heart Research

Workshops of the American Section of the International Society for Heart Research will be held in Burlington Vermont on June 17 through 20 1981 For further information contact Dr Norman Alpert Professor of Physiology College of Medicine University of Vermont Burlington Vt 05401

Conference and Symposium on Cardiac Arrhythmias

The Second Teaching Conference and Symposium on Cardiac Arrhythmias entitled Mechanisms of Sudden Death will be held on June 15 through 19 1981 in Florence Italy The conference is sponsored by the Department of Medicine University of Oklahoma and by the Instituto di Ricerche Cardiovascolari of the University of Milan For further information contact Dr Benjamin J Scherlag Veterans Administration Medical Center 921 N E 13th St Oklahoma City Okla 73104 Telephone (405) 271-4742

1981 Subspecialty Examination in Cardiovascular Disease

Beginning in 1981 the American Board of Internal Medicine s Subspecialty Examination in Cardiovascular Disease will revert to the former fall date The pertinent dates for 1981 are

Registration Period January 1 1981 to April 1 1981

Examination Date November 10 1981

Deadline for Cancellation October 1 1981

For application forms contact American Board of Internal Medicine 3624 Market St Philadelphia Pa 19104 Telephone (215) 243 1500

formed on 41 acromegalic patients at Mayo in the 60 year period 1919 to 1978 of which 27 cases with adequate clinical data and tissue were included in this pathologic review of the heart in acromegaly Cardiomegaly was common (22 of 27 cases or 81%) and occurred in both hypertensive and nonhypertensive patients The mean heart weight (618 g) of 16 patients who died 10 or more years after the clinical onset of acromegaly was significantly higher ($p < 0.01$) than that (348 g) of 11 patients who died within 10 years of the clinical onset of the disease Disproportionate cardiomegaly (compared to visceromegaly) occurred in about one fourth to one third of the cases The enlarged hearts seldom exceeded 200% (that is twice) of the expected heart weights *according to* the patient s body weight and body length Apart from hypertension other conditions to which cardiomegaly in acromegaly has been attributed were uncommon in our series diabetes 15% (four of 27) significant coronary artery disease 11% (three of 27) and valvular heart disease 19% (five of 27) Myocardial hypertrophy (93% or 25 of 27) and interstitial fibrosis (85% or 23 of 27) were constantly observed Other histological findings which have not been noted in earlier studies included lymphomononuclear cell infiltrate or myocarditis (59% or 16 of 27) and small vessel disease of the myocardium (22% six of 27) Although controversial the possibility of a specific acromegalic cardiomyopathy cannot be discounted on the basis of the currently available evidence

REFERENCES

1 Marie P Sur deux cas d acromegalie hypertrophie singuliere non congenitale des extremites superieures inferieures et cephalique Rev Med Paris 6 797 1886
2 Huchard H Anatomie pathologique lesions et troubles cardiovasculaires de l acromegalie J Praticiens 9 249 1895
3 Fournier J B C Acromegalie et troubles cardiovasculaires Thesis Paris 1896 No 3
4 Cushing H and Davidoff L M The Pathological Findings in Four Autopsied Cases of Acromegaly with a Discussion of Their Significance Monograph 22 Rockefeller Institute for Medical Research 1927 pp 1 131
5 Courville C and Mason V R The heart in acromegaly Arch Intern Med 61 704 1938
6 Coggeshall C and Root H F Acromegaly and diabetes mellitus Endocrinology 26 1 1940
7 Hejtmancik M R Bradfield J Y and Herrmann G R Acromegaly and the heart A clinical and pathologic study Ann Intern Med 34 1445 1951
8 Balzer R and McCullagh E P Hypertension in acromegaly Am J Med Sci 237 449 1959
9 Hamwi G J Skillman T G and Tufts K C Jr Acromegaly Am J Med 29 690 1960
10 Gordon D A Hill F M and Ezrin C Acromegaly A review of 100 cases Can Med Assoc 87 1106 1962
11 Souadjian J V and Schirger A Hypertension in acromegaly Am J Med Sci 254 629 1967
12 Hirsch E Z Sloman J G and Martin F I R Cardiac function in acromegaly Am J Med Sci 257 1 1969
13 Wright A D Hill D M Lowy C and Fraser T R Mortality in acromegaly Q J Med (New Series) 39 1 1970
14 Silinkova Malkova F and Kolbel F Relationship between symptoms of acromegaly and its complications principally cardiovascular in 86 patients Acta Univ Carol Med 16 553 1970
15 Ferine C J and Aloia J Heart muscle disease in acromegaly Am J Med 48 530 1970
16 Aloia J F, Field R A The heart and the endocrine system *in* Cardiac and Vascular Disease Vol II edited by Conn H L and Horwitz O Philadelphia 1971 Lea & Febiger pp 1252 1261
17 Rabinowitz D Sper S I and Bledsoe T The pituitary gland *in* The Principles and Practice of Medicine edited by A M Harvey New York 1972 18th edition Appleton Century Crofts Inc pp 839 840
18 deGroot W J Cardiomyopathy associated with endocrine disorders, Cardiovasc Clin 4 319 1972
19 McGuffin W J Jr Sherman B M Roth J Gorden P Kahn R Roberts W C and Frommer P L Acromegaly and cardiovascular disorders a prospective study Ann Intern Med 81 11 1974
20 Jonas F A Aloia J F and Lane F J Evidence of subclinical heart muscle dysfunction in acromegaly Chest 67 190 1975
21 Harrison s Principles of Internal Medicine edited by Thorn G W Adams R D Braunwald E et al New York 1977 McGraw Hill Book Company Inc pp 1309
22 Martins J B Kerber R E Sherman B M Marcus M L and Ehrhardt J C Cardiac size and function in acromegaly Circulation 56 863 1977
23 Rossi L Thiene G Caregaro L Giordano R, and Lauro S Dysrhythmias and sudden death in acromegalic heart disease Chest 72 495 1977
24 Mather H M Boyd M J, and Jenkins J S Heart size and function in acromegaly Br Heart J 41 697 1979
25 Ludwig J Current Method of Autopsy Practice Philadelphia 1979 2nd edition W B Saunders Company pp 670 686
26 Davidoff L M Studies in acromegaly III The anamnesis and symptomatology in one hundred cases Endocrinology 10 461 1926
27 Sober A J Gorden P Roth J and AvRaskin T W Visceromegaly in acromegaly Arch Intern Med 134 415 1974
28 Evans H M Briggs J H and Dixon J S The Pituitary Gland 1 edited by Harris G W and Donovan B T London 1966 p 439
29 German W J and Flanigan W Pituitary adenomas A follow up study of the Cushing series Clin Neurosurg 10 72 1964
30 Levene G and Miller L C Acromegalic gigantism without cardiac enlargement report of a case J Clin Endocrinol 2 403 1942
31 Cohen J Role of endocrine factors in the pathogenesis of cardiac hypertrophy Circ Res 1(Suppl II) 345 1953
32 DeGrandpre R and Raab W Interrelated *hormonal*

factors in cardiac hypertrophy experiments in nonhyper tensive hypophysectomized rats Circ Res 1 345 1953
33 Curtarelli G and Ferri C Cardiomegaly and heart failure in a patient with prolactin secreting pituitary tumour Thorax 34 328 1979
34 Szakacs J E and Cannon A l norepinephrine myocar ditis Am J Clin Pathol. 30 425 1958
35 Szakacs J E Dimmette R M., and Cowart E C Jr Pathological implication of the catecholamines epineph rine and norepinephrine US Armed Forces Med J 10 908 1959
36 Szakacs J E and Mehlman B Pathologic ch induced by l norepinephrine quantitative aspects, J Cardiol 5 619 1960
37 Kline I K Myocardial alterations associated pheochromocytomas Am J Pathol. 38 539 1961
38 Van Loon G R Abnormal plasma catechola responses in acromegalics J Clin Endocrinol M 48 784 1979

Copyright Information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner s consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients This consent is given on the condition however that the copier pay the stated per copy fee through the Copyright Clearance Center Inc 21 Congress Street Salem Mass 01970 617 744 3350 for copying beyond that permitted by Sections 107 or 108 of the U S Copyright Law This consent does not extend to other kinds of copying such as copying for general distribution for advertising or promotional purposes for creating new collective works or for resale

bject index*

A

pp 1 138 August pp 1 9 2 4 September pp 7 5-416 er pp 417 594 November pp 595-7 December Part 3-976 December Part pp 9 1096.

S

C

T

F

G

H

American Heart Journal

December 1980 Volume 100 Number 6 part 2

Introduction

The articles appearing in this issue were presented at the Symposium on Cardiac Arrhythmias A Decade of Progress—1980 held at Stanford University School of Medicine on May 8 9 and 10 1980 The conference provided a 10-year update on the first such symposium held in 1970 at Elsinor Denmark and featured many of the same participants The symposium as well as this publication were made possible by a generous educational grant from Astra Pharmaceutical Products Inc of Framingham Massachusetts These papers relate to new antiarrhythmic drugs and their comparative study and to other devices for managing patients with life-threatening ventricular arrhythmias unresponsive to treatment by drugs The complete transcript of the symposium will be published later in book form by G K Hall & Co Boston Massachusetts

In Section I Ronfeld Jewitt and Lawrie detail comparative data now available on new antiarrhythmic agents currently under investigation in Europe and the United States While these data are still incomplete for several of the new membrane-active drugs the summaries are the most comprehensive now available

Sections II and III outline studies in patients with coronary artery disease with tocainide an analog of lidocaine with Class I (membrane) activity The antiarrhythmic hemodynamic and toxicity data for patients with acute myocardial infarction demonstrate that tocainide is effective and safe Some patients do develop side effects but discontinuation of treatment is rarely required Long term administration of tocainide in patients with arrhythmias resistant to therapy with available agents is reported by Maloney and Winkle in Section III Horn summarizes safety data from the compassionate clearance protocol and Young presents the results of a series of planned protocols to evaluate tocainide's effectiveness

In Section IV Harrison Zipes Coumel and Schamroth describe their extensive experience with four other promising new antiarrhythmic agents encainide aprindine amiodarone and verapamil

In Section V the interaction of tocainide with beta blocking agents is discussed by Ikram Bigger presents convincing evidence that the Lown classification for premature ventricular contractions has many shortcomings and thus is not helpful in studying newer antiarrhythmic agents Griffin and Mirowski describe early experiences with implantable devices for detecting and electrically terminating arrhythmias

The 1970s truly represented a decade of progress in arrhythmia research New and sophisticated methods for detecting arrhythmias have been developed Pharmacokinetics has become an accepted clinical science and provides us with a more rational means for administering antiarrhythmic agents Drugs with different mechanisms of action have been introduced for trial and offer the hope of effective and safe prophylaxis and treatment of malignant arrhythmias Improved electrophysiologic study techniques have provided understanding of arrhythmia mechanisms and supply a means of designing circuitry for detection and electrical termination of arrhythmias

The 1980s no doubt will see substantial additional progress and excitement in this developing field

Donald C Harrison MD

0002-8703/80/1309— + 01500 10/0 © 1980 The C V Mosby Co

Comparative pharmacokinetics of new antiarrhythmic drugs

Robert A Ronfeld, Ph D *Framingham Mass*

The importance of pharmacokinetics to drug therapy is routinely accepted by many clinicians and especially cardiologists today Certainly the pharmacokinetics of a drug are a consideration when a dosage regimen is being designed for a drug and may even be a factor when a choice in drug therapy is being made A working knowledge of a drug s pharmacokinetics can be essential in cardiology since the kinetics of the drug may be altered by the patient s disease state or affected by the multiplicity of drugs the patients may be receiving

The objective of this report is to review the pharmacokinetics of several new antiarrhythmic agents Unfortunately there is a paucity of data on some of the new and possibly significant drugs For the most part these data have been abstracted from the literature Certainly in the coming years, as new analytic techniques are developed much of these data will be modified or viewed as incorrect The basic principles of pharmacokinetics will not be reviewed here since these have been covered satisfactorily in a recent review on antiarrhythmics

The pharmacokinetics of the established antiarrhythmics lidocaine quinidine and procainamide will not be reviewed in detail Because of their short half lives neither of these prototypes has been satisfactory for once or twice daily administration Therefore on the basis of half life alone a new antiarrhythmic agent could be a therapeutic improvement Al o in the steady state each of these three dru h [illegible] metabolite level th it could contribute to their [illegible] erall activity The presence of an active metab [illegible] lite [illegible] ertain ly will make the interpretation of clinical blood or plasma samples more difficult Active metabolites may also increase the interpatient dose response variability In the future there will very likely be a number of antiarrhythmics for the clinician to select from The predictability and convenience of a dosage regimen may then be an important consideration in selecting an appropriate dru

Tocainide

Tocainide and lidocaine have similar pharmacologic and electrophysiologic properties Tocainide is less potent than lidocaine in direct cardiac effects and in central nervous system (CNS) effects Tocainide is a primary amine in contrast to the tertiary amine lidocaine and consequently the free base is 20 times less lipophilic in an octanol water system

Aside from potency the major difference between lidocaine and tocainide resides in their pharmacokinetics Tocainide has a 11 to 13-hour half life in healthy volunteers In patients the mean half life was also 13 hours although the variability was greater than with the volunteers [5] The plasma protein binding of tocainide was constant over the therapeutic range with approximately 50% bound The renal clearance of free drug was approximately equivalent to the expected glomerular filtration rate Typically 40% of an oral dose is excreted unchanged in the urine and 25% is excreted as a glucuronide conjugate of *N* carboxytocainide Total body clearance in both patients and volunteers was 110 to 140 ml/min [5]

Plasma levels above 5 μg/ml are reported to be effective in reducing the frequency of premature ventricular beats Plasma concentrations above 5 0 and 8 3 μg/ml resulted on the average in 70% and 90% reductions in premature beats Other

Reprint requests Robert A R[illegible] Ph D [illegible] Astra Pharmaceutical Pr[illegible] Inc [illegible] MA 01[illegible]

[illegible] The C V Mosby Co

L

workers reported a 75% reduction in ventricular premature beats when the mean peak blood level was 10 3 µg/ml[7]

There are measurable levels of two metabolites in plasma the previously mentioned glucuronide and lactoxylidide which is the product of oxidative deamination[5] Based on animal pharmacologic data it appears that the metabolites do not contribute to the efficacy or CNS side effects of tocainide

Mexiletine

Mexiletine is a primary amine structurally similar to tocainide Mexiletine has an ether linkage between the benzene ring and alkyl chain whereas tocainide has an amide linkage Because of this structural difference mexiletine has a higher pK and much larger octanol water partition coefficient

The half life of mexiletine was 9 to 12 hours in volunteers In patients mean half lives of 12 and 13 hours were reported as well as a mean of 16 7 hours for patients with acute myocardial infarction The volume of distribution was large and reported as 6 6 and 8 1 L/kg in patients and 500 to 660 L in volunteers Total body clearance was also large at 6 5 and 7 1 ml/min/kg There are conflicting reports on the importance of renal excretion At a normal and unadjusted urinary pH 8% to 20% was excreted unchanged However at a urine pH of 5 renal excretion increased to 40% to 60% and renal clearance increased by a factor of 3 to 4 However the effect of normal physiologic variation in pH remains controversial At least in acute myocardial infarction (AMI) patients there were large intersubject variations in plasma levels with trough levels varying by an order of magnitude[1] The oral absorption and plasma levels were significantly reduced when mexiletine was concomitantly administered with morphine or diamorphine This negative effect on absorption is probably not unique for mexiletine and these investigators suggested that this may also occur with other drugs and antiarrhythmics

Effective plasma levels are reported to be 0 75 to 2 0 µg/ml The incidence of side effects including nausea tremor and hypotension increased at plasma levels above 2 0 µg/ml Mexiletine has been used both intravenously and orally and in the early stages of myocardial infarction Assuming it is effective there is an advantage to using the same drug for initial intra en u dar n tion and mainten ance oral admini tra n I t tunately becau e of the narrow the ape range the intravenous dosage schedu e are plex

Lorcainide

Lorcainide is a new antiarrhythmic in which there have only been preliminary reports on its electrophysiologic and antiarrhythmic p oper ties However the pharmacokinetics of this new antiarrhythmic have been reported in detail

The terminal half life in patients with chronic ventricular premature contractions was reported to be 7 7 hours by two separate groups of investigators There were dramatic differences among subjects with half lives varying from 2 6 to 15.2 hours The volume of distribution was very large at 8 to 10 L/kg The plasma and blood clearances were 1 000 and 1 500 ml/min respectively Only a few percent of the dose was excreted unchanged in the urine Since the clearance is approximately equivalent to liver blood flow we would expect a large first pass effect if metabolism occurs in the liver Based on a single 100 mg oral dose this assumption would appear correct since only 4% of the dose was bioavailable However the bioavailability increased to 30% to 60% with a 200 mg dose and increased to 45% to 200% with multiple 100 mg doses Apparently metabolic saturation occurs with oral administration There are probably two factors contributing to this the concentration presented to the liver can be much higher after an oral dose than after an intravenous dose and at least with multiple dosing there may be product or metabolite inhibition This dose-dependent bioavailability may also occur with drugs such as propranolol and alprenolol which also have high hepatic clearances

The primary metabolite in plasma appears to be a N dealkylated lorcainide or norlorcainide At steady state the norlorcainide lorcainide ratio is approximately 3 with oral administration and 1 with intravenous administration The activity of both compounds measured either as reduction in ventricular premature contractions (VPCs) or QRS widening was similar An effective antiarrhythmic dose appears to be around 100 mg t i d which resulted in steady tate plasma levels of 300 and 900 ng/ml for lorcainide and norlorcainide respectively

M

Aprindine

Aprindine is a Class I antiarrhythmic agent and local anesthetic. It has electrophysiologic properties similar to lidocaine but exhibits greater potency. In two separate studies with volunteers the average half life was 22 hours with a range of 12 to 66 hours.[23] However in patients average half lives of 43 and 50 hours with ranges of 20 to 110 hours were found.[4] Analysis of the data from one volunteer study, in which both cold and radiolabeled drugs were administered, implicated a 70% to 80% bioavailability.[1] This apparently was due to first pass metabolism since the total radioactivity in the plasma was identical for both oral and intravenous doses. The total body clearance in volunteers was approximately 170 ml/min or 2.5 ml/min/kg. In patients it appears to be substantially lower, possibly around 70 ml/min.

Plasma levels effective in suppressing supraventricular or ventricular arrhythmias were generally from 1 to 2 μg/ml. Minor side effects, most frequently dizziness, occurred in the 2 to 3 μg/ml range. Primary metabolites reported have been hydroxylation on the phenyl and indanyl rings and desethylaprindine.[4]

Disopyramide

Disopyramide is an established antiarrhythmic with electrophysiologic properties similar to quinidine. Half lives in volunteers are generally reported to be 7.0 to 8.0 hours. However these half lives may not be real or meaningful since the plasma protein binding of disopyramide changes dramatically with concentration and even within the therapeutic range.

It has been reported that free fraction in plasma increased by 30% to 100% as total concentration increased over the therapeutic range. Because of the nonlinearity in protein binding total plasma concentration and area under the plasma curve are not proportional to dose. However the concentration of nonprotein bound drug in plasma was proportional to dose. It appears that clearance is solely dependent on free drug and consequently changes in protein binding do not affect the free concentration. The half life of the free drug in plasma has been reported to be [illegible] hours. Since the clearance of free drug is constant [illegible] the dose and concentration we would [illegible] changes in binding to be of any consequence [illegible] pharmacologic activity. However, this makes interpretation and dosage adjustment based on total plasma concentration very difficult. The determination of free concentration is not a routine procedure in most laboratories. The therapeutic range for disopyramide in terms of total concentration is reportedly 2 to 7 μg/ml.[3]

Disopyramide phosphate (Norpace) had an 80% to 90% [3,34,35] bioavailability when oral versus intravenous plasma levels were used as a criterion and 90% when urinary excretion was used.[3,36] Because of its short half life it is generally administered at 6 or 8 hour intervals. However a sustained release product has been developed which allows for a 12 hour dosage schedule.[36]

Approximately 50% to 60% of an intravenous or oral dose can be recovered as unchanged drug in the urine.[3,5] The major metabolite appears to be *N*-desisopropyldisopyramide, which accounts for another 25% of the dose in urine. At steady state the plasma levels of the metabolite were approximately one third of the parent compound.

Verapamil

Verapamil has been recognized as an antiarrhythmic agent for many years. Even before specific analytic methods were developed it was recognized that the drug was probably rapidly metabolized since the effective oral dose was 10 to 15 times the required intravenous dose.

Although there has been extensive work on the pharmacology and electrophysiology of this compound, there is a paucity of data on its pharmacokinetics. The only complete report indicates that it has a half life of 3 to 4 hours following a 10 mg intravenous dose. The total body plasma clearance in three subjects 59 to 69 years of age varied from 730 to 1,120 ml/min (mean 12.6 ml/min/kg). Only 5% of the dose was excreted unchanged in the urine. Although it was not done in a crossover fashion, the apparent bioavailability was only 10% to 20% following an 80 mg oral dose. This low availability was apparently due to a large first pass effect since, based on radioactivity, absorption was complete. The volume of distribution was large at 6.0 l/kg and the plasma protein binding was 90%.

As with other drugs with large hepatic clearances such as lorcainide and propranolol, we would expect a large intersubject variability in plasma levels following oral administration

N

O

P

Table I Pharmacokinetic parameters of antiarrhythmics in man

Antiarrhythmics	$T_{1/2}$ (hr)	Vd† (L/kg)	Clearance (ml/min/kg)	Bioavailability (%)	Renal excretion (%)	Reference
Quinidine	6 3	2 5	4 7	70	20	44
Procainamide	3 0	2 9	9 0	75	60	45
Lidocaine	1.8	1 6	10 0	30	5	46
Tocainide	13 0	2 8	2 4	95	40	See text
Mexiletine	13 0	6 6	6 6	85	10	See text
Aprindine	50 0	4 0	1 0	5	2	See text
Lorcainide	7 7	7 9	16 1	~200	2	See text
Verapamil	3 0	5 9	12 6	12	2	See text
Disopyramide						
Total	7 0	0 5	0 9	85	55	See text
Free	4 0					
Bretylium	7.8	1 3	1[illegible] 1	25	77	41
Flecainide	14 0			95		4[illegible]

$T_{1/2}$ = elimination half life
†Vd = apparent volume of distribution (Vd_{β} or Vd ...)

There are several metabolites with the N demethylated compound apparently the major metabolite in plasma At steady state this metabolite (norverapamil) and verapamil have approximately equivalent plasma levels It has been suggested that the therapeutic plasma levels are in the range of 100 to 400 ng/ml All of the metabolites are less potent than verapamil Norverapamil had the greatest potency with a 4 6 less vasodilating potency than verapamil

Summary

Table I lists pharmacokinetic parameters for eight of the drugs discussed as well as for quinidine procainamide and lidocaine Data for two of the new agents bretylium and flecainide were not discussed in the text If possible these values are from patients Obviously the individual values especially those in the critically ill patients may differ considerably from the mean values listed Also with a drug such as lidocaine there is a growing amount of evidence suggesting that clearance and the elimination rate constant decrease for patients receiving infusions longer than 24 hours

As stated earlier the three older drugs quinidine procainamide and lidocaine all have less than ideal pharmacokinetic properties for easily maintaining constant blood levels Of course one solution to this has been to develop sustained release dosage forms Of the new drugs listed tocainide mexiletine aprindine and flecainide all have high bioavailability and a half life that may allow for twice daily administration The feasibility of twice daily administration depends on the therapeutic range and the difference between the maximum and minimum concentrations For a half life of 12 to 14 hours we could expect a 1 5 to 2 0 ratio in maximum to minimum concentrations

With disopyramide a half life is listed for both free and total drug Also volume of distribution and clearance are given for total disopyramide in order to be consistent and comparable with the other drugs listed As discussed earlier the value for free disopyramide is the most meaningful

With both verapamil and lorcainide there is a potential for a large first pass metabolism However in the case of lorcainide apparent metabolic saturation results in an apparent 100% bioavailability

These pharmacokinetic data may or may not be used in a clinical setting Very possibly though a blood or plasma sample will be sent to the laboratory for drug analysis When obtaining a drug level questions to ask yourself or the laboratory might be (1) Is the value reliable was the assay method specific and could the blood sampling tube or technique lead to a false value? (2) How can these data along with other clinical and symptomatic data be used to stabilize or improve therapy?

REFERENCES

1 Harrison DC Meffin PJ Winkle RA Clinical pharmacokinetics of antiarrhythmic drugs Prog Cardiovasc Dis 20 217 19 7

Q

R

2 Lalka D Meyer MB Duce BR Elvin AT Kinetics of the oral antiarrhythmic lidocaine congener tocainide Clin Pharmacol Ther 19 757 1976
3 Graffner C Conradson T Hofrendahl S Ryden L Tocainide kinetics after intravenous and oral administration in healthy subjects and in patients with acute myocardial infarction Clin Pharmacol Ther 27 64 1980
4 Winkle RA Meffin PJ Fitzgerald JW Harrison DC Clinical efficacy and pharmacokinetics of a new orally effective antiarrhythmic tocainide Circulation 54 884 1976
5 Ronfeld RA Wolshin EM Block AJ Tocainide and metabolites Human pharmacokinetics and animal pharmacology Clin Pharmacol Ther 27 287 1980
6 Elvin AT Keenaghan JB Byrnes EW Tenthorey PA McMaster PD Takman BH Lalka D Manion CV Baer DT Wolshin EM Meyer MB Ronfeld RA Tocainide conjugation in humans Novel biotransformation pathway for a primary amine J Pharm Sci 69 47 1980
Ryan W Engler R, LeWinter M Karliner JS Efficacy of a new oral agent (tocainide) in the acute treatment of refractory ventricular arrhythmias Am J Cardiol 43 285 1979
8 Prescott LF Pottage A Clements JA Absorption distribution and elimination of mexiletine Postgrad Med J 53(Suppl 1) 50 1977
9 Campbell NPS Kelly JG Adgey AAJ Shanks RG Mexiletine in normal volunteers Br J Clin Pharmacol 6 [illegible] 1978
10 Campbell NPS Kelly JG Adgey AAJ Shanks RG The clinical pharmacology of mexiletine Br J Clin Pharmacol 6 103 1978
11 Haalman ACA Roos JC Siebelink J Dunning AJ Development of a dosage scheme for simultaneous intravenous and oral administration of mexiletine Postgrad Med J 53(Suppl 1) 128 1977
12 Kiddie MA, Kaye CM Turner P Shaw TRD The influence of urinary pH on the elimination of mexiletine Br J Clin Pharmacol 1 229 1974
13 Johnston A Burgess CD Warrington SJ Wadsworth J Hamer NAJ The effect of spontaneous changes in urinary pH on mexiletine plasma concentrations and excretion during chronic administration to healthy volunteers Br J Clin Pharmacol 8 349 1979
14 Pottage A Campbell RWF Achuff SC Murray A Julian DC Prescott LF The absorption of oral mexiletine in coronary care patients Eur J Clin Pharmacol 13 393 1978
15 Carmeliet E Janssen PAJ Marsboom R van Neuten JM Xhonneux R Antiarrhythmic electrophysiological and hemodynamic effects of lorcainide Arch Int Pharmacodyn Ther 231 104 1978
16 Jähnchen E Bechtold H Kasper W Kersting F Just H Heykants J Meinertz T Lorcainide I Saturable presystemic elimination Clin Pharmacol Ther 26 18 1979
17 Klotz U Muller-Seydlitz P Heimburg P Pharmacokinetics of lorcainide in man A new antiarrhythmic agent Clin Pharmacokinet 3 407 1978
18 Shand DG Rangno RE The disposition of propranolol I Elimination during oral absorption in man Pharmacology 7 [illegible] 1972
19 Ablad B Ervik M Hallgren J Johnsson G Solvell L Pharmacological effect and serum levels of orally administered alprenolol in man Eur J Clin Pharmacol 5 44 1972
20 Meinertz T Kasper W Kersting F Just H Bechtold H Jähnchen E Lorcainide II [illegible] concentration effect relationship Clin Pharmacol Ther 26 [illegible] 1979
21 Klotz U Muller-Seydlitz P Heimburg P Disposition and antiarrhythmic effect of lorcainide Int J Clin Pharmacol Biopharm 17 152 1979
22 Delcroix C Martin L, Van Durme JP Kesteloot H, Hagemeijer F Mbuyamba P Deblecker M Model for exchange kinetics of aprindine in man after single and multiple doses Acta Cardiol Suppl 18 177 1974
23 Dodion L, de Suray JM Deblecker M Georges A Caracteristiques pharmacocinetiques et biodegradation de l'aprindine chez l'homme Therapie 29 [illegible] 1974
24 Hagemeijer F Absorption half life and toxicity of oral aprindine in patients with acute myocardial infarction Eur J Clin Pharmacol 9 71 1975
25 Van Durme JP Bogaert MG Rosseel MT Therapeutic effectiveness and plasma levels of aprindine a new antidysrhythmic drug Eur J Clin Pharmacol 7 341 1974
26 Murphy PJ Metabolic pathways of aprindine Acta Cardiol Suppl 18 131 1974
27 Ranney RE Dean RR Karim A Radzialowski FM Disopyramide phosphate Pharmacokinetic and pharmacologic relationships of a new antiarrhythmic agent Arch Int Pharmacodyn 191 162 1971
28 Bryson SM Whiting B Lawrence JR Disopyramide serum and pharmacologic effect kinetics applied to the assessment of bioavailability Br J Clin Pharmacol 6 409 1978
29 Hinderling PH Bres J Garrett ER Protein binding and erythrocyte partitioning of disopyramide and its mono-dealkylated metabolite J Pharm Sci 63 1684 1974
30 Cunningham JL, Shen DD Shudo I Azarnoff DL The effects of urine pH and plasma protein binding on the renal clearance of disopyramide Clin Pharmacokinet 2 373 1977
31 Meffin PJ Robert EW Winkle RA Harapat S Peters FA Harrison DC Role of concentration-dependent plasma protein binding in disopyramide disposition J Pharmacokinet Biopharm 7 29 1979
32 Hinderling PH Garrett ER Pharmacokinetics of the antiarrhythmic disopyramide in healthy humans J Pharmacokinet Biopharm 4 199 1976
33 Niarchos AP Disopyramide Serum level and arrhythmia conversion AM HEART J 92 57 1976
34 Cunningham JL, Shen DD Shudo I Azarnoff DL The effect of non linear disposition kinetics on the systemic availability of disopyramide Br J Clin Pharmacol 5 343 1978
35 Dubetz DK Brown NN Hooper WD Eadie MJ Tyrer JH Disopyramide pharmacokinetics and bioavailability Br J Clin Pharmacol 6 279 1978
36 Forssell G Graffner C Nordlander R Nyquist O Comparative bioavailability of disopyramide after multiple dosing with standard capsules and controlled release tablets Eur J Clin Pharmacol 17 [illegible] 1980
37 Krikler DM Verapamil in cardiology Eur J Cardiol 2 1 1974
38 Schomerus M Spiegelhalder B Stieren B Eichelbaum M Physiological disposition of verapamil in man Cardiovasc Res 10 605 1976
39 Woodcock BG Hopf R Kaltenbach M Verapamil and norverapamil plasma concentrations during long term therapy in patients with hypertrophic obstructive cardiomyopathy J Cardiovasc Pharmacol 2 1 1980
40 Neugebauer G Comparative cardiovascular actions of verapamil and its major metabolites in the anaesthetised dog Cardiovasc Res 12 247 1978
41 Narang PK Adir J Yacobi A Josselson J Sadler JH Twenty-seventh National Meeting Academy of Pharmaceutical Sciences Nov 11 [illegible] Kansas City M[illegible]

xperimental and laboratory reports

pex and subxiphoid approaches to Ebstein's nomaly using cross-sectional chocardiography

adashi Kambe M D
atoshi Ichimiya M D
Iasao Toguchi M D
ono Hibi M D
oichi Fukui M D
inya Nishimura M D
obuo Sakamoto M D
asuo Hojo M D
agoya Japan

he diagnosis of Ebstein s anomaly is in typical ases easily suspected from physical findings ogether with electrocardiography and x ray xamination In milder forms of the anomaly owever the diagnosis may be difficult without dditional invasive technics such as angiocardiog aphy [1] The lesion shows considerable variation in he pathologic anatomy of the malformation nd its clinical manifestations [3] Since its dvent M mode echocardiography has served as useful tool for the diagnosis of Ebstein s anom ly [1-6] although it is not suitable for the spatial rientation of cardiac structures

Cross sectional echocardiography has also pro vided various clinical information on cardiac natomy and movements Recently apex cross ectional echocardiography has been introduced to display four cardiac chambers side by side[10-1] and a subxiphoid approach has been added to conventional M mode[13-4] or cross sectional echo cardiography [15]

The aim of this study is to describe the abnor malities of the tricuspid valve in Ebstein s anomaly and the chordae tendineae in the right side of the heart using apex and subxiphoid cross sectional echocardiography

Materials and methods

Cross sectional echocardiography was per formed on 11 patients with Ebstein s anomaly isolated or associated with other heart diseases as shown in Table I They ranged in age from two to 43 years Five patients were male and the remain der were female The diagnosis was confirmed by right heart catheterization and angiocardiogra phy in 10 patients and the remaining one was diagnosed by clinical findings and noninvasive diagnostic technics including echocardiography One patient underwent cardiac surgery Two out of the 11 patients showed slight to moderate cyanosis For the control 10 patients with atrial septal defect of secundum type were similarly examined in addition to 10 normal subjects

Cross sectional echocardiograms were obtained by a commercially available Sonolayergraph of Toshiba SSH 11A [1] This instrument was charac terized by its electronic sector scanning system with a wide angle (78 degrees) and 32 element phased array Its resonant frequency was 2 4 MHz The scanning speed was 30 cross sections per second and one frame was composed of 112 scanning lines Furthermore it was possible to simultaneously record dual beam M mode echo cardiograms by sampling from the cross sectional

From the Third Department of Internal Medicine and Pediatrics, Nagoya University School of Medicine Nagoya J pan

Supported in part by the Japanese Ministry of Education
Received fo public t on Dec 19 1978
Accepted for publicat n April 19 1979

Reprint requests Tadashi Kambe M D The Third Department of Internal Medicine Nagoya Univers ty School of Medicine 65 Tsuru mai cho Showa ku N goya J pan 466

000?-8703/80/070053 + 06$00 60/0 © 1980 The C V Mosby Co

Table I Displacement of the septal tricuspid leaflet*

Case no	Name	Sex	Age	Cardiac diagnosis	Displacement of STL (cm)
1	H. S	m	35	Ebstein s anomaly	3.2
2	T I	m	29	Ebstein s anomaly	2.0
3	F A	m	5	Ebstein s anomaly + PFO	2.2
4	M T	f	5	Ebstein s anomaly + ASD	N.A.
5	Y N	f	2	Ebstein s anomaly + PFO	1 6
6	T T	f	25	Ebstein s anomaly + PS + ASD	N.A.
7	K. N	f	4	Ebstein s anomaly	1 4
8	J N	m	38	Ebstein s anomaly	2.4
9	A. L	f	21	Ebstein s anomaly + PFO	2.2
10	M. S	m	22	Ebstein s anomaly	N.A.
11	R. W	f	43	Ebstein s anomaly	1.8

In eight of the 11 patients it was measured in the four-chamber view from the same plane as the anterior mitral leaflet to the root of the septal tricusp leaflet in end-diastole, using 8 mm cinematography

Abbreviations m = male f = female PFO = patent foramen ovale ASD = atrial septal defect PS = pulmonic stenosis STL = septal tricusp leaflet N.A. = not available

images The effective diagnostic depth was 16 cm

The two dimensional images were obtained in the supine position by directing the cross sectional planes through the cardiac apex and subxiphoid area

Fig 1 shows the position of the transducer and the direction of the ultrasonic beam An apical four chamber view was obtained by orienting the transducer from the cardiac apex in the direction *A*

This cross section readily provided a four chamber view so as to permit visualization of the interventricular septum connected with the interatrial septum in the middle of the images with both ventricles and atria side by side

An apical three chamber view was recorded by orienting the transducer in the direction of *B* which was nearly perpendicular to the cross sectional plane A for the apical four chamber view This cross section provided a three chamber view of the right side of the heart namely the atrialized and functional right ventricles and the right atrium eliminating the left sided heart chambers

Furthermore a subxiphoid cross section was obtained by placing the transducer horizontally below the xiphoid process *C* and occasionally along the left costal margin *D* to visualize the wider area encompassing the right ventricular cavity to the left sided heart

Results

Our data were divided into two major categories the first was the assessment of the downward displacement of the septal tricuspid leaflet in a four chamber view through the cardiac apex and the second was the subxiphoid approach to the evaluation of the subvalvular apparatus such as the chordae tendineae inserting into the tricuspid valve

1 Apex cross section

a *Four chamber view* An apical four chamber view was obtained in all the patients Fig 2 shows a four chamber view by apex cross section in a 35 year old male (H S) with Ebstein s anomaly The septal tricuspid leaflet *(STL)* is displaced downward into the right ventricle resulting in the formation of the atrialized right ventricle *(AT RV)* and functional right ventricle *(FRV)* The anterior tricuspid leaflet *(ATL)* is elongated but not displaced from the tricuspid valve ring Fig 3 shows another example of the four chamber view in a 21 year-old female patient with Ebstein s anomaly and patent foramen ovale The STL is similarly displaced downward into the right ventricular cavity

The displacement of the STL was measured in the four chamber view from the same plane as the anterior mitral leaflet *(AML)* to the root of the STL in end-diastole using 8 mm cinematography The displacement ranged from 1 4 to 3 2 cm with an average of 2 1 ± 0 5 cm in eight patients as shown in Table I However the downward deviation of the STL could not be measured in three patients in the four chamber view In one of these three patients (M T) the rudimentary STL was detected by angulating the probe in the direction *B* as shown in Fig 1 In contrast the four chamber view disclosed no displacement of

4? Conard GJ Carlson GL, Frost JW Ober RE Human pla ma pharmacokinetics of flecainide acetate (R-818) a new antiarrhythmic following single oral and intrave nous doses. Clin Pharmacol Ther 25 218 19 9
43 Le Lorier J Grenon D Latour Y Caille G Dumont G Brosseau A Solignac A Pharmacokinetics of lidocaine after prolonged intravenous infusions in uncomplicated myocardial infarction Ann Intern Med 87 700 1977
44 Ueda CT Hirschfeld DS Scheinman MM Rowland M Williamson BJ Dzindzio BS Disposition kinetics of quinidine Clin Pharmacol Ther 19 30 1976
45 Galeazzi RL Benet LZ Sheiner LB Relationship between the pharmacokinetics and pharmacodynamics of procainamide Clin Pharmacol Ther 20 2 8 1976
46 Thom on PD Melmon KL, Richard on JA Cohn K Steinbrunn W Cudihee R Rowland M Lidocaine pharmacokinetics in advanced heart failure liver disease and renal failure in humans Ann Intern Med 78 499 1973

280 patients. Entry into the study was 2 weeks after acute myocardial infarction (AMI). Patients were followed up for 1 year. Ventricular arrhythmias totally disappeared in 50% of aprindine patients and in 20% of the placebo group. There was no difference in death rate between the two groups. Cholestasis (three patients) and agranulocytosis (two patients) appeared in the aprindine group. Somewhat similar results have been presented by Hutton using tocainide. A comparable study with mexilitine, conducted by Julian et al (personal communication, 1979), has also shown the same type of result, that is, reduction or abolition of ventricular arrhythmias compared with placebo therapy but no significant reduction in death rate.

Amiodrone

Amiodrone is a Class III drug that is reputed to be effective against ventricular fibrillation. It has also been shown to be especially useful in the long term prophylaxis of Wolff Parkinson White syndrome and ventricular arrhythmias, but certain side effects (corneal deposits and dysfunction of thyroid gland) have inhibited its general use. There is no published information regarding its efficacy compared with any of the preceding new antiarrhythmics.

Verapamil

Verapamil, a Ca antagonist, is useful in the acute management of supraventricular tachycardias in acute myocardial ischemia or ventricular arrhythmias. Once again there have been no comparative trials with verapamil and the other newer antiarrhythmic agents, particularly in ventricular arrhythmias.

Discussion

The reduction or abolition of ventricular arrhythmias achieved with various drugs, such as mexilitine, tocainide, and aprindine, without an accompanying reduction in death rate is rather disappointing, indicating that the effectiveness of an antiarrhythmic agent against so-called warning ventricular arrhythmias does not mean that they are effective against VF or sudden death. On the other hand, it is interesting to note that effectiveness against sudden death in postinfarct patients has been claimed for several agents (not regarded as antiarrhythmic agents), such as sulfinpyrazone, aspirin, and persantin. The explanation for this divergence of results remains to be elucidated.

Summary

A number of new antiarrhythmic drugs have been introduced in the past decade. They have been extensively studied, mainly in patients with AMI and for short periods following this event. No long term comparative trials have been reported, although some medium term studies have been completed and longer term studies are underway. Most of the new agents have been demonstrated to be effective in diminishing or suppressing serious ventricular arrhythmias, but this has not been associated with a corresponding fall in the death rate. To date none of these drugs, except perhaps beta blockers, has been shown to lower the risk of sudden death. Nevertheless, the question remains as to whether a small reduction in the mortality rate warrants widespread use of any of the current drugs for the prevention of sudden death. There is a great need for long term comparative trials with patients properly stratified to see which agent is most effective and in what particular patient group.

REFERENCES

1. Snow PJD. Effect of propranolol in myocardial infarction. Lancet 2:551, 1965.
2. Balcon R, Jewitt DE, Davies JPH, Oram S. A controlled trial of propranolol in acute myocardial infarction. Lancet 2:915, 1966.
3. Clausen J, Felsby M, Jorgensen FS, Neilsen BL, Roin J, Strange B. Absence of prophylactic effect of propranolol in myocardial infarction. Lancet 2:920, 1966.
4. Multicentre trial. Propranolol in acute myocardial infarction. Lancet 2:1435, 1966.
5. Barber JM, Boyle DMcC, Chatgurvedi HC, Singh N, Walsh MJ. Practolol in acute myocardial infarction. Ulster Med J 36:127, 1967.
6. Sloman G, Stannard M. Beta adrenergic blockade and cardiac arrhythmias. Br Med J 4:508, 1967.
7. Kahler RL, Brill SJ, Perkins WE. *In* Kattus AA, Ross G, Hall VE, editors: Cardiovascular beta adrenergic responses. Los Angeles, 1968, University of California Press, p 213.
8. Norris RM, Caughey DE, Scott PJ. A trial of propranolol in acute myocardial infarction. Br Med J 2:398, 1968.
9. Fucella LM. Quoted by Sowton E, in Prog Cardiovasc Dis 10:561, 1968.
10. Barber JM, Boyle D McC, Chatgurvedi MC, Singh N, Walsh MJ. Practolol in acute myocardial infarction. Acta Med Scand (Suppl.) 587:213, 1975.
11. Norris RM. Letter to editor. Lancet 2:1090, 1978.
12. Reynolds JL, Whitlock RML. Effects of a beta adrenergic receptor blocker in myocardial infarction treated for one year from onset. Br Heart J 34:252, 1972.
13. Wilhelmsson C, Vedin JA, Wilhelmsen L, Tibblin G, Werko L. Reduction of sudden deaths after myocardial

Hemodynamic effects of newer antiarrhythmic drugs

David E Jewitt MB *London England*

The aim of antiarrhythmic drug therapy is to terminate or suppress specific arrhythmias and improve cardiovascular function Short term studies of the new Class I drugs encainide mexiletine and tocainide have demonstrated only minor falls in cardiac index with modest rises in mean aortic pressure In contrast disopyramide has been shown to depress myocardial function in both animals and patient studies Heart failure may be precipitated by therapy with disopyramide and electromechanical dissociation has been reported Class II agents with beta adrenergic blocking actions all produce a degree of myocardial depression Atenolol resembles propranolol in patients with coronary artery disease in its hemodynamic effects whereas acebutolol is less of a depressant resembling practolol The Class III agent amiodarone has only a mild depressant effect associated with a reduction in afterload and an increase in coronary blood flow The Class IV agent verapamil which is a calcium channel blocker has potent myocardial depressant actions and causes peripheral vasodilatation Hypotension heart failure and shock have been precipitated particularly in patients receiving beta blocking drugs concurrently While all the new antiarrhythmic drugs currently studied will cause some degree of hemodynamic depression in an appropriately high concentration present investigations suggest that particular caution needs to be taken when disopyramide aprindine atenolol and verapamil are administered either acutely by the intravenous route or chronically by the oral route

The aim of successful antiarrhythmic drug therapy is to terminate or suppress a specific arrhythmia and improve cardiovascular function This action may be achieved by the suppression or termination of arrhythmias that are either directly life threatening or the precipitating cause of cardiovascular failure An ideal antiarrhythmic drug will achieve this objective without general or cardiovascular side effects in therapeutic dosage It is important therefore to document the hemodynamic effects of newer antiarrhythmic drugs at clinically relevant concentrations and to confirm that when arrhythmia termination is achieved cardiovascular function is not compromised These studies need to be performed in patients with heart disease with and without evidence of impaired cardiac function

In this report the hemodynamic effects of newer antiarrhythmic drugs will be reviewed in groups according to their predominant experimental electrophysiologic effect as described in the classification of antiarrhythmic drugs by Vaughan Williams[1] and Singh and Vaughan Williams

From the Cardiac Department King's College Hospital London England

Reprint requests David E Jewitt [illegible] Cardiac Department King's College Hospital [illegible] Hill London [illegible] United Kingdom

Drugs with Class 1 antiarrhythmic action

Mexiletine The influence of mexiletine on left ventricular ejection in patients with abnormal left ventricular function was assessed in six patients with implanted Starr Edwards aortic valve prostheses The duration of aortic ball travel time measured as the QA_1 interval is a measure of left ventricular ejection velocity and was used as an index of myocardial performance With myocardial depression the QA_1 interval lengthens Shaw showed that mexiletine in doses from 50 to 150 mg given intravenously over 2 minutes prolonged the QA interval in a dose related manner over the range 50 to 150 mg and this effect was apparent immediately It was equal to that produced by equivalent doses of lignocaine indicating similar effects on left ventricular function Banim et al in a study of 10 male patients with coronary artery disease found

0002-8703/80/120984 + 08$00.80/0 © 1980 The C. V. Mosby Co

infarction by treatment with alprenolol Lancet 2 1157 1974
14 Ahlmark G Saetre H Korsgren M Reduction of sudden deaths after myocardial infarction Lancet 2 1563 1974
15 A Multicentre International Study Improvement in prognosis of myocardial infarction by long term beta adrenoreceptor blockade using practolol Br Med J 2 735 1975
16 Baber NS Wainwright Evans D Howitt G Thomas M Wilson C Two multi centre propranolol post infarction trial in 84 hospital in the United Kingdom Italy and Yugoslavia Br Med J 1980 (In press)
17 Vedin JA Wilhelmsson CE A review of current beta blocker trials in the world Hart Bull 10 180 1979
18 Oshrain C Editorial Disopyramide phosphate (Norpace) A new antiarrhythmic drug Circulation 59 2 1979
19 Van Durme JP Bogaert M Bekaert I De Clercq D Moerman E Comparison of the antidysrhythmic efficacy of atenolol disopyramide mexilitine and placebo Symposium on Management of Ventricular Tachycardia Copenhagen 1978 Excerpta Medica pp 581
20 Jennings G Jones MBS Besterman EMM Model DG Turner PP Kidner PH Oral disopyramide in prophylaxis of arrhythmias following myocardial infarction Lancet 1 51 1976
21 Ross D Vohra J Sloman JC Disopyramide in myocardial infarction Lancet 1 330 1978
22 Podrid PJ Schoeneberger A Lown B Congestive heart failure caused by oral disopyramide N Engl J Med 302 614 1980
23 Talbot RG Nimmo J Julian DC Clark RA Neilson JMM Prescott LF Treatment of ventricular arrhythmias with mexilitine Lancet 2 399 1973
24 Stavenow L Hanson A Johansson BW Mexiletine in treatment of ventricular arrhythmias Acta Med Scand 205 411 1979
25 Hagemeijer F van Durme JP Lubsen J Bogaert M Hugenholtz PG The Ghent Rotterdam aprindine study Antiarrhythmic prophylaxis after myocardial infarction Proceedings of the International Conference on Myocardial Infarction Florence 1979 (In press)
26 Rosenbaum MB Chiale PA Ryba D Elizari MV Control of tachyarrhythmias associated with Wolff Parkinson White syndrome by amiodarone hydrochloride Am J Cardiol 34 215 1974

an infusion of 1.5 mg/kg mexiletine had minor effects on cardiovascular hemodynamics only. There was a small but significant rise in left ventricular end-diastolic pressure. During hand grip isometric exercise, there were small but significant falls in cardiac output and peak left ventricular dP/dt associated with a small increase in left ventricular end-diastolic pressure. This lack of major hemodynamic effect was confirmed in studies of 16 patients with valvar heart disease.[4] In contrast, Saunamaki observed further impairment of myocardial function in three of six patients with ischemic heart disease and previous heart failure who were given mexiletine intravenously, achieving a plasma level greater than 1 $\mu g/ml$.

In many respects mexiletine is comparable to lignocaine hemodynamically when given intravenously. It is concluded that intravenous administration of mexiletine in clinically effective doses produces little or no adverse hemodynamic effects in the absence of clinical evidence of heart failure. When heart failure is present, caution is necessary during its intravenous administration. In controlled studies of long term oral mexiletine in the prophylaxis of ventricular arrhythmias over a 3-month period, there has been no evidence that cardiac failure was precipitated.

Disopyramide. A negative inotropic effect has been demonstrated when disopyramide is administered intravenously to experimental animals and man. Thus in a placebo controlled study in 18 patients with recent myocardial infarction, 100 mg of disopyramide intravenously over 5 minutes significantly prolonged the pre-ejection period and increased the ratio of the pre-ejection period to left ventricular ejection time for more than 15 minutes following drug administration. However, if the rate of administration of the same dose was prolonged over 10 minutes, a reduced effect was seen.

In a study of 10 patients with cardiac disease (six with normal and four with abnormal left ventricular function), 1.5 mg/kg of intravenous disopyramide over 2 minutes decreased cardiac index, stroke volume, and stroke work index to a greater degree in those patients with abnormal function, both during spontaneous sinus rhythm and when heart rate was maintained stable by atrial pacing.

In a recent study, electromechanical dissociation has been reported following the administration of disopyramide to patients with severe congestive failure and renal insufficiency in whom the drug was being administered to control recurrent and resistant ventricular tachycardia. This indicated the need for dosage reduction in the presence of renal insufficiency and extreme caution. The importance of hemodynamic depression following disopyramide administration was demonstrated when 16 patients with disopyramide induced cardiac decompensation were reported out of a total of 100 patients consecutively treated with the drug.

Whereas in patients without established left ventricular dysfunction, disopyramide is relatively safe orally, the intravenous route should be used with caution. In the presence of left ventricular dysfunction, disopyramide is potentially a hazardous agent not only intravenously but also during chronic oral therapy, and careful clinical observation is mandatory.

Tocainide. In a study of 12 patients with established heart disease, 11 of whom had compensated left ventricular dysfunction, small increases in left ventricular end diastolic pressure have been noted, although no major depression of overall ventricular function was seen with tocainide plasma concentrations within the known therapeutic range. An increase in systemic and pulmonary arterial pressure was observed in this study, secondary to increases in vascular resistance in both beds. In patients with valvar heart disease studied echocardiographically in a control study of oral tocainide, no evidence of myocardial depression was observed.

Tocainide therefore, like lignocaine and mexiletine, appears to cause minimal myocardial depression at therapeutic plasma concentrations. Further information on the hemodynamic effects of tocainide are reported elsewhere in this symposium.

Encainide. This new antiarrhythmic agent has been shown electrophysiologically to have important Class 1 actions.[2] Hemodynamically, it has been studied in patients at the time of catheterization by Harrison.[11] In this study, 17 patients were given encainide intravenously, 12 of whom had coronary artery disease and 5 of whom had primary myocardial disease. There was a significant increase in heart rate and systemic vascular resistance following encainide 0.9 mg/kg body weight intravenously with a modest decrease in cardiac and stroke index. Left ventricular end

II Evaluation of antiarrhythmic drugs in acute myocardial infarction

Placebo controlled study of prophylaxis of ventricular arrhythmias in acute myocardial infarction

Ronald W F Campbell M D *Newcastle upon Tyne England*

Successful prophylaxis of ventricular arrhythmias in acute myocardial infarction m ght ach eve a major reduction in mortal ty of this condition No sat sfactory drug is yet ava lable but many new antiarrhythmic agents are being tested in this role Such placebo controlled investigations in the earl est phase of myocardial infarction encounter unique problems of study design drug pharmacokinetics study conduct and data analysis

Identification of a safe effective antiarrhythmic drug for the prophylaxis of ventricular arrhythmias associated with acute myocardial infarction is currently an important goal of cardiologic research A placebo controlled study is generally considered the optimal design for evaluation of new therapies and is probably essential in this clinical situation which is associated with high natural mortality and morbidity rates but the complex and rapidly changing pathophysiology of acute myocardial infarction presents particular difficulties in the design conduct and analysis of placebo controlled investigations

Objectives and justification of placebo controlled studies

The aim of a placebo controlled study for the prophylaxis of ventricular arrhythmias in acute myocardial infarction is to define an antiarrhythmic drug which by preventing serious ventricular arrhythmias might improve morbidity or mortality rates Ventricular fibrillation and hemodynamically significant ventricular tachycardia are the arrhythmias of particular importance in this context The study should clearly identify patients for whom therapy was beneficial and evaluate drug safety in all treated individuals

Administration of a placebo to patients with acute myocardial infarction is acceptable only if there is no active agent of proved benefit that is being withheld because of the study Propranolol lidocaine and disopyramide have been reported to reduce the mortality rate in acute myocardial infarction Further investigations with propranolol failed to confirm the original findings The study of intramuscular lidocaine was flawed by a statistically significant excess of patients who received active therapy and a further investigation of lidocaine given by this route failed to show benefit The findings of the study of disopyramide have been the subject of considerable criticism and cannot be accepted until further corroborative investigations are reported

A statistically significant reduction of primary ventricular fibrillation by means of high dose intravenous lidocaine has been reported The hospital mortality rate was unaffected Although there is no corroborative controlled study evidence uncontrolled investigations appear to support the original conclusions However an earlier investigation using intravenous lidocaine documented an increased evidence of A V conduction disorders producing prolonged ventricu

From th Uni rsit D partment of Card ology F eem n Hosp t l Newcastl upon Tyn E gl nd

Repri t requests R n ld W F Campbell, M D Sen Lecture in Cli ic l C rd ol gy Freeman Hosp tal Freem n Road High H at n Newca tle-upon Tyne United Kingdom

0002 8703/80/130995 + 05$00 50/0 © 1980 The C V Mosby Co

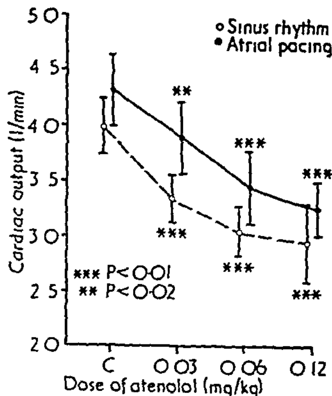


Fig 1 Mean changes in cardiac output in patients receiving graded doses of atenolol during sinus rhythm and during atrial pacing at constant rate (From Robinson C Jackson PG Fisk C J with DF Haemodynamic effects of atenolol in patients with coronary artery disease Br Heart J 40 22-8 1978

diastolic pressure fell significantly Changes in cardiac index were most marked in the nine patients with low control cardiac index levels The mild depression seen mainly in patients with impaired cardiac function at rest suggests that this drug s hemodynamic effects will not detract from its potential value However more information is required on the effects of this drug intravenously and orally on systemic and coronary hemodynamics in patients with established heart disease with and without prior left ventricular dysfunction

Drugs with Class 2 antiarrhythmic actions

The hemodynamic effects of propranolol have been extensively investigated in the past and it has become the agent against which all new Class 2 antiarrhythmic drugs with beta blocking actions are compared Hemodynamically practolol has been shown intravenously to be an effective antiarrhythmic drug producing less hemodynamic depression However development of the oculomucocutaneous syndrome following its oral use has restricted its subsequent therapeutic value although it remains a useful agent intravenously in intensive and coronary care units Several new beta adrenergic blocking drugs all with comparable antiarrhythmic value particularly in the management of supraventricular arrhythmias have been introduced Here attention will be limited to two such agents atenolol and acebutolol

Atenolol Atenolol has been shown to possess cardioselectivity equivalent to that of practolol and like practolol atenolol lacks membrane-stabilizing properties In contrast however atenolol does not possess intrinsic sympathomimetic activity [15] Its antiarrhythmic efficacy has been established in animal studies Its hemodynamic effects have been studied in a group of eight patients with established obstructive coronary artery disease [1]

A dose related decrease in heart rate and cardiac output was shown to be produced without a significant change in systemic arterial pressure when atenolol, 0 03 to 0 12 mg/kg body weight intravenously was given over a total of 6 to 10 minutes (Fig 1) However in contrast to the previous findings with practolol and like those observed with propranolol there was a significant fall in cardiac output after atenolol which was not purely rate dependent (Fig 1) Left ventricular end diastolic pressure did not change significantly but there was a dose related reduction in the maximum rate of rise of left ventricular pressure (dP/dt) after atenolol Systemic vascular resistance increased significantly after atenolol in the patients at rest and this is comparable to the findings after intravenous propranolol but contrasts with those after intravenous practolol in similar patients [1]

The overall hemodynamic effects of atenolol therefore more closely resemble those of intravenous propranolol than those of intravenous practolol It seems likely that the relatively minor hemodynamic effects that follow intravenous practolol reflect the combination of cardioselectivity and intrinsic sympathomimetic activity in the same agent whereas cardioselectivity alone as in atenolol results in hemodynamic effects similar to those of propranolol Atenolol is therefore of potential value as an antiarrhythmic drug orally but does not have the hemodynamic advantages of practolol for intravenous administration

Acebutolol Acebutolol is a newer beta adren

lar asystole in lidocaine treated patients who were suspected of having sustained infarction but in whom this diagnosis was not later confirmed[11]

The lack of a safe effective antiarrhythmic drug for the prophylaxis of ventricular arrhythmias in patients suspected of acute myocardial infarction justifies continued placebo controlled studies of prophylactic antiarrhythmic therapy

Study design

Study population In clinical practice an acceptable effective drug for the prophylaxis of ventricular arrhythmias would be given to a relatively unselected patient population with suspected acute myocardial infarction However the high early incidence of ventricular arrhythmias in acute myocardial infarction[1] allows identification of patients who are at particular risk and therapy may be more economically evaluated by restricting administration to this group

Shock cardiac failure and conduction disorders are common reasons for exclusion of patients from studies It is probably not justified to expose such patients to the risk of antiarrhythmic therapy that may aggravate these complications of acute myocardial infarction Other acceptable conditions of exclusion include situations where the pharmacokinetics of the drug may be grossly abnormal e g in patients with hepatic or renal disease Care must be exercised to minimize the exclusion criteria or therapy will be evaluated in such a restricted patient population that the findings will have little practical applicability

Predefined serious ventricular arrhythmias (ventricular fibrillation and hemodynamically significant ventricular tachycardia) death and possible unwanted effects of therapy or infarction are premature end points of study and usually involve withdrawal of the patient Patients who are protocol violations should also be withdrawn when it is recognized that they have not satisfied the entry criteria They will have received inappropriate therapy and it is essential that any consequences of drug administration to them be reported Nonconfirmation of infarction is the most common cause for early withdrawal This is usually unavoidable as it is desirable that selected patients be admitted into the investigation as soon as possible after identification However within the first few hours after the onset of symptoms definite confirmation of acute myocardial infarction is available for only a few patients since the ECG often will show no or nonspecific ST changes and enzyme levels are not usually available instantly In consequence a placebo controlled study employing early randomization of patients will probably include a sizable proportion who in retrospect have no sustained acute myocardial infarction but whose progress in the study cannot be neglected

Therapeutic considerations Prophylactic interventions against serious ventricular arrhythmias particularly primary ventricular fibrillation, must be rapid in their onset In theory intravenous administration of a drug could achieve near instantaneous therapeutic plasma levels but in practice this is difficult to accomplish and toxic effects are often encountered An additional disadvantage is the need for skilled medical or paramedical attendance to establish this route of administration By contrast intramuscular administration can be undertaken by unskilled people and even by the patient himself with a pressurized injector and by using a suitable site therapeutic plasma levels can be obtained almost as quickly as with intravenous therapy The maintenance of an adequate plasma level of the drug after the initial intramuscular administration can present difficulties and may involve additional intramuscular administration or recourse to either intravenous or oral doses Oral therapy has the attraction of easy administration but gastrointestinal absorption may be slow and reduce the effectiveness of the drug Both acute myocardial infarction and the management of its pain by narcotic analgesia reduce the rate of gastric emptying thus delaying drug absorption[11] This factor probably precludes the successful use of oral antiarrhythmic therapy in reducing the incidence of serious ventricular arrhythmias in acute myocardial infarction

The duration of administration of therapy can vary from a few hours to many days or even months If the prophylaxis of primary ventricular fibrillation is the major objective of the study then the duration of therapy might be confined to the first 24 hours after the onset of symptoms since thereafter the incidence of this arrhythmia is low Continuation of therapy beyond the first 24 hours after the onset of symptoms permits examination of the drugs effect on the arrhyth

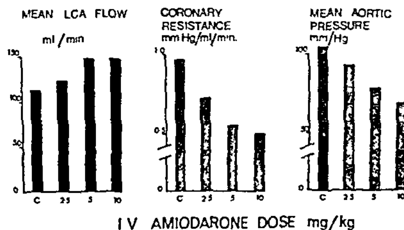


Fig 2 Mean coronary hemodynamic changes following graded doses of intravenous amiodarone in eight open-chest anesthetized dogs LCA = left coronary artery

ergic blocking drug that has been shown to be approximately one-eighth as potent as propranolol as a beta antagonist It exerts membrane stabilizing effects similar to those of propranolol It does have a degree of cardioselectivity and also some intrinsic sympathomimetic activity although less marked than that seen with practolol Hemodynamically in doses of 0.6 to 1 mg/kg it has been shown to cause modest reductions in cardiac output and ejection fraction when administered postoperatively to patients who have undergone coronary artery bypass surgery

In a recent study in patients with obstructive cornary artery disease acebutolol in doses of 0.6 mg/kg body weight intravenously given over 2 minutes produced only minor systemic hemodynamic effects The changes in coronary sinus blood flow and coronary vascular resistance were also minor and there was no significant change in myocardial oxygen consumption It is important to note that the lactate extraction ratio in these patients during control atrial pacing to angina was −14% ± 4.5% indicating lactate production This was reversed to lactate extraction with a mean value 10% [illegible] 2 at the same atrial pacing rate after the drug Acebutolol therefore resembles practolol more closely than propranolol or atenolol hemodynamically It is likely that this reflects the possession of both weak intrinsic sympathomimetic activity and cardioselective properties It is a useful alternative to practolol when an intravenous beta blocking drug is indicated for the termination of supraventricular arrhythmias

Drugs with Class 3 antiarrhythmic actions

Amiodarone Amiodarone originally introduced as an antianginal drug is the principal agent with Class 3 properties and possesses unique electrophysiologic properties Its antiarrhythmic effects were summarized by Rosenbaum et al The effects of amiodarone on cardiac and coronary hemodynamics were studied in open-chest anesthetized dogs by Singh et al Intravenous amiodarone over the concentration range of 2.5 to 10 mg/kg body weight produced a dose related decrease in heart rate and total peripheral resistance with a decrease in cardiac contractile force and left ventricular dP/dt Despite this the left ventricular cardiac output increased progressively No significant fall in left ventricular end-diastolic pressure occurred up to doses of 5 mg/kg body weight intravenously but at 10 mg/kg intravenously modest increases in left ventricular filling pressure occurred These findings in association with the fall in left ventricular contractile force and left ventricular dP/dt suggested a modest negative inotropic effect The increase in cardiac output with increasing doses probably reflects the marked reduction in resistance to left ventricular ejection which results from the systemic vasodilatation

mias encountered in this later phase of infarction but few of these rhythm disturbances will be of a life threatening type

Conduct of the study

Informed consent The value and medicolegal significance of informed consent is controversial [3] but is essential and appropriate for the majority of clinical research investigations None theless it is questionable whether it is justified to seek informed consent from patients with acute myocardial infarction when they require rest sedation relief of pain and reassurance rather than an academic discourse on the implications of enrollment into a placebo controlled prophylactic antiarrhythmic drug study Informed consent implies a patient s understanding of the conventional alternative to the proposed study However there is no standardized arrhythmia management high dose prophylactic intravenous lidocaine aggressive treatment of warning arrhythmias and management only of hemodynamically significant arrhythmias are three diverse but widely practiced approaches Perhaps in acute myocardial infarction protocol approval by fellow practitioners and ethical committees extensive elective drug testing in a variety of clinical situations and the propriety and compassionate concern of the investigating physician could reduce the necessity for informed consent

Arrhythmia data acquisition and analysis As the early high mortality rate of acute myocardial infarction largely reflects primary ventricular fibrillation it is possible to design a study that does not require continuous recording or monitoring of the ECG However most studies do employ some form of ECG analysis Following the demonstration of the inaccuracy of observer monitoring of the ECG continuous ECG recording and sophisticated analysis is commonplace These recordings can present particular analysis difficulties as the changing shape of the QRS ST and T waves associated with acute infarction can cause false triggering of arrhythmia analyzers which must also cope with a high incidence of artifact due to the restlessness of the patient sweating and poor adhesion of electrodes Continuous ECGs must contain clear identification of at least the time of drug administration and should preferably record clock time continuously throughout the study

Use of drugs The study medication would be the only drug administered in an ideal prophylactic antiarrhythmic investigation but in practice this is rarely the case Restriction of the use of additional antiarrhythmic therapy is however highly desirable The role of the coronary care unit in the monitoring and rapid treatment of significant arrhythmias assumed greater importance with the suggestion that a variety of ventricular arrhythmias appeared to predict the development of ventricular fibrillation and that suppression of these events could abort ventricular fibrillation ' Were this true then aggressive suppression of these ventricular arrhythmias would be justified and the task of evaluating drugs for the prophylaxis of ventricular fibrillation might be made easier as reduction of these events could be a criterion of drug effectiveness However warning arrhythmias appear not to foretell ventricular fibrillation and have been reported as frequently in patients who do not progress to ventricular fibrillation as in those who do The justification for treating these arrhythmias then is their hemodynamic consequence which is probably insignificant for isolated ventricular ectopic complexes of almost any frequency multiform ventricular ectopic complexes ventricular ectopic complex pairs R on T ventricular ectopic complexes and perhaps short runs of ventricular tachycardia If these arrhythmias can be tolerated without treatment the attendant reduction in use of antiarrhythmic drugs would greatly improve the evaluation of prophylactic antiarrhythmic drugs Sustained or hemodynamically significant ventricular arrhythmias such as ventricular fibrillation or prolonged episodes of ventricular tachycardia require treatment when they occur

Other hemodynamically significant arrhythmias that may require intervention include atrial fibrillation atrial flutter sinoatrial disorders and A V conduction problems which can be a consequence of infarction but which should be considered as potential unwanted effects of the study medication Similarly bundle branch block and QRS complex axis shifts should be noted although attitudes vary regarding the need for immediate management or for withdrawal from a prophylactic antiarrhythmic drug study

Antiarrhythmic drugs are not the only drugs that can interfere with the evaluation of antiar

Direct intracoronary injections of amiodarone 0 25 to 4 mg which were doses too small to exert systemic effects produced a dose related increase in coronary blood flow associated with a fall in coronary vascular resistance This coronary vasodilator effect was also seen during intravenous amiodarone injections in doses of 2 5 to 10 mg/kg body weight In this instance the increasing coronary blood flow and fall in coronary vascular resistance was achieved despite a fall in systemic arterial pressure (Fig 2) Experimentally therefore amiodarone creates a favorable balance in oxygen supply and demand by affecting the major determinants of myocardial oxygen consumption These experimental observations have since been confirmed in 16 patients undergoing coronary arteriography for chest pain 14 of whom had obstructive coronary artery disease

These clinical studies therefore confirm that amiodarone used intravenously is a powerful systemic and coronary vasodilator and is relatively safe for use in the acute therapy of patients with cardiac arrhythmias However antiarrhythmic therapy with amiodarone is generally indicated and most effective by the oral route To date long term hemodynamic studies using this route of administration have not been published however there are no reports of cardiac failure being precipitated

Drugs with Class 4 antiarrhythmic actions

Verapamil The prototype of this group of agents that selectively inhibit membrane transport of calcium is verapamil It is a synthetic papaverine derivative initially introduced as a smooth muscle relaxant which has potent peripheral and coronary vasodilator actions In isolated heart muscle it does not exhibit Class 1 2 or 3 electrophysiologic actions and therefore a separate category of action emphasizing the antagonism of the slow inward calcium currents was proposed Its main locus of action appears to be superficially located membrane storage sites for calcium In clinical electrophysiology its primary site of action is on the A V node where A V conduction time is increased du   depression of the slow response fibers

Verapamil has a marked negative inotropic effect on isolated heart muscle In man the most comprehensive study of its hemodynamic effects was reported by Singh and Roche In 20 patients with coronary artery disease or rheumatic valve lesions they found the peak effects of intravenous verapamil in a dose of 10 mg occurred between 3 and 5 minutes after the completion of the injection and had disappeared by 10 minutes Mean arterial pressure and systemic vascular resistance fell significantly with an increase in left ventricular end-diastolic pressure and a reduction in left ventricular dP/dt_m Heart rate and cardiac index increased but these changes were not statistically significant These results therefore indicated that intravenously verapamil does have a negative inotropic effect but it is minimized by its peripheral vasodilator action in reducing afterload Caution is clearly necessary particularly when verapamil is administered to patients with significant myocardial decompensation and in patients with myocardial infarction as in these patients there are little data available on the hemodynamic effects of the drug

The incidence of hemodynamic side effects is much higher in patients previously on beta adrenergic blocking agents who are given verapamil either intravenously or orally The negative inotropic actions and depressant effects on impulse generation of the beta blocking agents and those of verapamil summate Severe hypotension coupled with bradycardia and asystole may result

The administration of verapamil intravenously is therefore potentially hazardous in the presence of impaired left ventricular function and particularly where prior administration of beta adrenergic blocking drugs has been employed In the absence of left ventricular impairment the mild hemodynamic changes observed are unlikely to be clinically important

REFERENCES

1 Vaughan Williams EM Classification of antiarrhythmic drugs *In* Sandoe E Flensted Jensen E Olesen KH editors Symposium on cardiac arrhythmias Sweden 1970 Astra Pharmaceutical Product Inc
2 Singh BN Vaughan Williams EM A fourth class of anti-dysrhythmic action? Effect of verapamil on ouabain toxicity on atrial and ventricular intracellular potential and on other features of cardiac function Cardiovasc Res 6 109 19 1972
3 Shaw TRD The effect of mexiletine on left ventricular ejection A comparison with lignocaine and propranolol Postgrad Med J 53 (Suppl) [illegible] 1977
4 Campbell NPS Zaidi SA Adgey AAJ Patterson GC Pantridge JF Observations of hemodynamic effect of mexiletine Br Heart J 41 [illegible] 1979
5 Banim SO Da Silva A Stone D Balcon R Observations of the haemodynamics of mexiletine Postgrad Med J 73(Suppl 1) 74 7 1977

rhythmic therapy The variety of clinical problems encountered in acute infarction encourages the use of drugs and of those commonly administered narcotic analgesics diuretics potassium supplements antiemetics hypnotics sedatives tranquilizers atropine digoxin and beta adrenergic blocking drugs may all modify the natural course of ventricular arrhythmias, including ventricular fibrillation and may alter the effect of the antiarrhythmic drug under investigation Many protocols have failed to standardize or establish criteria for the use of these therapies and often reports have omitted information regarding the incidence of use of these drugs during the study

Termination of the study At the termination of a prophylactic controlled study all data of all patients should be analyzed before allocation codes are broken unless a sequential statistical approach has been adopted A theoretic possibility exists that a patient who has received active therapy may be at particular risk of arrhythmias on termination of therapy either by exposure of a previously suppressed event or by a rebound phenomenon Clinical experience suggests that this problem is not significant

Analysis of data

Group comparability The many risk factors related to the natural history of acute myocardial infarction should be balanced in both placebo and active therapy groups Age sex site of acute myocardial infarction time from onset of symptoms to inclusion in the study estimates of infarct size smoking history the number of previous myocardial infarctions and previous therapy are among those commonly examined The time from the onset of symptoms to inclusion in the study is probably the most important feature and is usually recorded for each group as a mean time with the standard deviation However this type of comparison can conceal important imbalances between patient groups and these are relevant in considering ventricular arrhythmias which are critically time dependent A profile of the number of patients admitted within defined time periods from the onset [illegible] would allow better comparison

Analysis of patients who have [illegible] sustained acute infarction All patients [illegible] placebo controlled study of antiarrhythmic therapy in acute myocardial infarction [illegible] rted in the final analysis Those who are entered [illegible] who are shown not to have sustained acute myocardial infarction will have received inappropriate therapy It might be anticipated that an active drug would have little or no beneficial effect in these patients who probably have a low risk of developing serious ventricular arrhythmias, but these individuals may be particularly susceptible to the adverse effects of the study drug In addition, the dose and route of administration of the active drug will have been chosen to achieve rapid therapeutic plasma levels in patients with acute myocardial infarction but the pharmacokinetics of the drug may be markedly different in patients without this diagnosis Analysis of nonmyocardial infarction patients should include documentation of the incidence not only of unwanted symptoms but also of cardiac failure sinoatrial disorders A V conduction disorders shock and analysis of ventricular arrhythmias as performed for those patients with definite acute myocardial infarction

Extrapolation of results Although tempting, it is not justified to extrapolate that a drug highly effective in suppressing ventricular tachycardia will be useful in the prevention of ventricular fibrillation Primary ventricular fibrillation and ventricular tachycardia have distinctly different time courses in acute myocardial infarction and their mode of initiation is strikingly different

Conclusions

Since 1961 there have been over 14 placebo controlled studies of antiarrhythmic therapy in acute myocardial infarction The drugs investigated have included procainamide [illegible] quinidine [illegible] propranolol [illegible] lidocaine [illegible] disopyramide [illegible] mexiletine,[illegible] and tocainide [illegible] Few have restricted inclusion to patients seen in the earliest hours of infarction and analysis of events in nonmyocardial infarction patients has been rare There is no standardized study design for the placebo controlled investigation of prophylactic antiarrhythmic drug therapy in acute myocardial infarction but improved knowledge of the natural history of arrhythmias in acute infarction and awareness of the practical difficulties and implications of identifying a successful management dictate careful consideration of the many special aspects of research of this clinical problem

I would like to acknowledge the a[illegible]sance of Miss I Kilkenny in the preparation of the manuscript

Saunamaki KI Hemodynamic effects of a new antiarrhythmic agent mexiletine in ischemic heart disease Cardiovasc Res 9 788 9? 197?

Hillis WS Tweddel A Lorimer AR Lawrie TDV Some aspects of the clinical pharmacology of intravenous disopyramide after myocardial infarction J Int Med Res 4(Suppl) 4 1976

Sutton R Hemodynamics of intravenous disopyramide J Int Med Res 4(Suppl) 46 8 1976

Desai J Hirschfeld D Peters R Scheinman M Gonzalez R Electromechanical dissociation associated with disopyramide Circulation 58(Suppl II) 1 8 19 8

Podrid PJ Schoenberger A Lown B Congestive cardiac failure caused by oral disopyramide N Engl J Med 302 614 7 1980

Winkle RA Anderson F Peters F Meffin PG Fowles RE, Harrison DC The hemodynamic effects of intravenous tocainide in patients with heart disease Circulation 57 787 9? 19 8

Ryan WF Karliner JS Effects of tocainide on left ventricular performance at rest and during acute alterations in heart rate and systemic arterial pressure Br Heart J 41 175-81 1979

Gibson JK, Somani P Bassett AL Electrophysiological effects of encainide on canine Purkinje fibers Eur J Pharmacol 52 161-69 1978

Harrison DC Winkle R, Sami M Mason J Encainide A new and potent antiarrhythmic agent AM HEART J 100 1046-1054 1980

Jewitt DE Hemodynamic side effects of antiarrhythmic drugs *In* Sandoe E Flensted-Jensen E Olesen KH editors Symposium of cardiac arrhythmias Sweden 19 0 Astra Pharmaceutical Products Inc

Barrett AM Carter J Fitzgerald JD Hull R Le Count D A new type of cardioselective adrenoceptive blocking drug Br J Pharmacol 48 340 1973

16 Robinson C Jackson PG Fluck C Jewitt DE Haemodynamic effects of atenolol in patients with coronary artery disease Br Heart J 40 2? ? 197?

17 Jewitt DE Mercer CJ Shillingford JP The circulatory effects of practolol in patients with acute myocardial infarction. Cardiovasc Res 4 188-93 19 0

18 Mason JW Specter JM Ingels MB Daughters GT Fernn AC Alderman EL Haemodynamic effects of acebutolol Br Heart J 40 29-34 1978

19 Daly K Bergman G Atkinson L Jackson G Jewitt DE Systemic and coronary hemodynamic effects and changes in myocardial metabolism produced by acebutolol. Br Heart J (In press)

20 Singh BN Jewitt DE, Downey JM Kirk ES R Sonnenblick EH Effects of amiodarone and L8040 novel antianginal and antiarrhythmic drugs on cardiac and coronary haemodynamics and on cardiac intracellular potentials Clin Exp Pharmacol Physiol 3 4 7-4 19 6

21 Rosenbaum MB Chiale PA Halpern MS Nau GJ Przybylski J Levi RJ Lazzari JO Elizari MV Clinical efficacy of amiodarone as an antiarrhythmic agent Am J Cardiol 38 934 1976

22 Coté P Bourassa MG Delaye J Janin A Froment R David P Effects of amiodarone on cardiac and coronary haemodynamics and on myocardial metabolism in patients with coronary artery disease Circulation 59 1165- 2, 19 9

23 Naylor W Krikler D Verapamil and the myocardium. Postgrad Med J 50 441-46 1974

24 Singh BN Roche AHG Effects of intravenous verapamil on haemodynamics in patients with heart disease AM HEART J 94 593-99 1977

REFERENCES

1 Snow PJD Effect of propranolol in myocardial infarction Lancet 2 551 1965
2 Valentine PA Frew JL Mashford ML, Sloman JG Lidocaine in the prevention of sudden death in the pre-hospital phase of acute infarction N Engl J Med 291 1327 31 1974
3 Zainal N Carmichael DJS Kidner PH Gillham AD Summers GD Oral disopyramide for the prevention of arrhythmias in patients with acute myocardial infarction admitted to open wards Lancet 2 887 9 1977
4 Balcon R, Jewitt DE Davies JPH Oram S A controlled trial of propranolol in acute myocardial infarction Lancet 2 917 24 1966
5 A Multicentre Trial Propranolol in acute myocardial infarction Lancet 2 1435 7 1966
6 Lie KI Liem KL, Louridtz WL Janse MJ Willebrands AF Durrer D Efficacy of lidocaine in preventing ventricular fibrillation within 1 hour after a 300 mg intramuscular injection A double blind randomized study of 300 hospitalized patients with acute myocardial infarction. Am J Cardiol 42 486 8 19 8
7 Dollery CT Krikler DM Shillingford JP Disopyramide in myocardial infarction Lancet 2 1185 19 7 (Letter)
8 Julian DG Disopyramide in myocardial infarction Lancet 2 1369 1977 (Letter)
9 Lie KI Wellens HJJ Von Capelle FJ Durrer D Lidocaine in the prevention of primary ventricular fibrillation N Engl J Med 29 1324 6 1974
10 Wyman MG Hammersmith L Comprehensive treatment plan for the prevention of primary ventricular fibrillation in acute myocardial infarction Am J Cardiol 33 661 , 19 4
11 Mogensen L Ventricular tachyarrhythmias and lignocaine prophylaxis in acute myocardial infarction Acta Med Scand (Suppl)513 1-80 1970
1 Adgey AAJ Allen JD Geddes JS James RGG Webb SW Zaida SA Pantridge JF Acute phase of myocardial infarction Lancet 2 501-4 1971
13 Prescott LF Pharmacokinetic abnormalities in myocardial infarction *In* Sandoe L, Julian DG Bell JW editors Management of ventricular tachycardia—role of mexiletine vol. 458 Amsterdam 19 8 Excerpta Medica pp 465 71
14 Cassileth BR Zupkis RV Sutton Smith K March V Informed consent—why are its goal imperfectly realized? N Engl J Med 302 896 900 1980
15 Rennie D Informed consent by well nigh abject adults N Engl J Med 302 917 8 1980
16 Romhilt DW Bloomfield SS Chou T Fowler NO Unreliability of conventional electrocardiographic monitoring for arrhythmia detection in coronary care units Am J Cardiol 31 457 61 19 3
17 Vetter NJ Julian DG Comparison of arrhythmia computer and conventional monitoring in coronary care unit Lancet 1 1151-4 1975
18 Murray A Campbell RWF Julian DG Artifactual and morphological difficulties encountered in the automatic analysis of ambulatory ECG recordings *In* Sandoe L, Julian DG Bell JW editors Management of ventricular tachycardia—role of mexiletine vol. 458 Amsterdam 1978 Excerpta Medica pp 349-57
19 Lown B Fahkro AM Hood WB The coronary care unit New perspectives and directions JAMA 199 188 1967
20 Lie KI Wellens HJJ Downar E Durrer D Observations on patient with primary ventricular fibrillation complicating acute myocardial infarction Circulation 52 755 9 1975
21 El Sherif N Myerburg RJ Scherlag BJ Befeler B Aranda JM Castellanos A Lazzara R Electrocardiographic antecedents of primary ventricular fibrillation Br Heart J 38 415 22 19 6
22 Campbell RWF Relation of ventricular arrhythmias to primary ventricular fibrillation Br Heart J 43 100 1980
23 Koch Weser J Klein SW Foo Canto LL, Kastor JA DeSanctis RW Antiarrhythmic prophylaxis with procainamide in acute myocardial infarction N Engl J Med 281 1253-60 1969
24 Bloomfield SS Romhilt DW Chou T Fowler NO Quinidine for prophylaxis of arrhythmias in acute myocardial infarction N Engl J Med 285 979-86 1971
25 Bennett MA Wilner JM Pentecost BL Controlled trial of lignocaine in prophylaxis of ventricular arrhythmias complicating myocardial infarction Lancet 2 909 11 1970
26 Pitt A Lipp H Anderson ST Lignocaine given prophylactically to patients with acute myocardial infarction Lancet 1 612 5 1971
27 Chopra MP Thandani U Portal RW Aber CP Lignocaine therapy for ventricular ectopic activity after acute myocardial infarction Br Med J 3 668 70 1971
28 Jennings G Jones MBS Besterman FMM Model DG Turner PP Kidner PH Oral disopyramide in prophylaxis of arrhythmias following myocardial infarction Lancet 1 51-4 19 6
29 Campbell RWF Achuff SC Pottage A Murray A Prescott LF Julian DG Mexiletine in the prophylaxis of ventricular arrhythmias during acute myocardial infarction J Cardio Pharm 1 43 5? 19 9
30 Campbell RWF Bryson LG Bailey BJ Murray A Julian DG Oral tocainide in suspected acute myocardial infarction Circulation 70(Suppl 2) 59 60 19 9

Comparison of newer antiarrhythmic agents

T D V Lawrie M D *Glasgow Scotland*

In the past decade a number of new antiarrhythmic drugs have been introduced They have been extensively used in the acute phase of myocardial infarction Few if any long term comparative trials of these newer agents have been reported Most of these newer agents have been shown to be able to reduce the frequency of ventricular arrhythmias but not the mortality rate Beta blockers and some antiplatelet adhesive drugs however have reduced the mortality rate following myocardial infarction There is a need for long term properly stratified trials of these effective agents

The main aim of chronic antiarrhythmic therapy is to reduce or prevent the occurrence of ventricular fibrillation (VF) and sudden death thus reducing the mortality rate Certain antiarrhythmic agents such as quinidine procainamide and phenytoin have been extensively studied—especially in coronary heart disease where VF and sudden death are most common Quinidine has been shown to decrease ventricular ectopic beats (VEBs) in acute myocardial infarction but there is no convincing evidence that it has materially reduced the mortality rate from sudden death in such patients in the long term in fact in some patients it has been shown to precipitate VF In contrast procainamide does appear to have a favorable effect not only in reducing the frequency of VEBs but also the frequency of sudden death A major problem resulting from its long term use however is its ability to produce a systemic lupus erythematosus-like syndrome in a large proportion of patients Phenytoin appears to be less effective than procainamide in preventing serious ventricular arrhythmias

Furthermore the numerous studies involving these drugs have shown that the dosage schedule for each drug requires adjustment for each individual patient and side effects are not infrequent There is therefore a need to look for newer antiarrhythmic agents that not only diminish or suppress ventricular arrhythmias but also prevent VF and sudden death have a simple dosage regime and have few or no side effects when taken over a prolonged period

There is a dearth of information on long term comparative trials of the new antiarrhythmic agents It is therefore necessary to review the various publications on each agent and thereby try to gain some knowledge about their relative efficacy

From the Uni [illegible] Departme [illegible] Royal Infirmary Glasgow Scotland

Reprint requests T D V Lawrie [illegible] University of Medical [illegible]

Beta blocking agents

Although beta adrenergic blocking agents have been in use for 10 to 15 years mainly for the treatment of angina pectoris and hypertension, they may also be regarded as falling into the category of newer antiarrhythmic agents Practolol alprenolol oxprenolol and propranolol have been used in long term secondary prevention studies following acute myocardial infarction To date the results of 15 studies in Europe have been reported In 11 of the studies[1-11] the agent was started within 24 to 48 hours of the clinical onset of infarction In the remaining four studies treatment was started 2 weeks or more after the onset of infarction[1-1] It is not possible to summarize in this presentation the results of all of these studies which varied in design selection of patients and duration of treatment Furthermore the effect of the particular agent on preventing sudden death as opposed to reinfarction is not clear from the presentation of results We propose to discuss briefly the major studies with positive findings

The results of the multicenter practolol study

000-8703/80 130990 + 0 500 [illegible] The C V Mosby Co

Hemodynamic and antiarrhythmic effects of tocainide in patients with acute myocardial infarction

Olof Nyquist M D Gunilla Forssell M D Rolf Nordlander M D and Karin Schenck Gustafsson M D *Stockholm Sweden*

In order to evaluate the hemodynamic and antiarrhythmic efficacy of tocainide studies were performed in patients suffering acute myocardial infarction Intravenous tocainide was administered over a 15 minute period in order to determine its acute effects and subsequently in a randomized double blind study with placebo control to determine its effects over a 24-hour period in acute myocardial infarction Tocainide resulted in a significant decrease of frequent and complex ventricular arrhythmias acutely and had only minimal effects of hemodynamics in most patients In the long term studies tocainide produced no adverse hemodynamic effects when compared with placebos

Tocainide is a new antiarrhythmic drug that is chemically similar to lidocaine but in contrast is *effective in the treatment of* ventricular arrhythmias when given orally[1-4] Although some of the patients in previously reported studies had coronary artery disease the antiarrhythmic circulatory and adverse effects of tocainide have not been evaluated in patients with acute myocardial infarction (AMI) As tocainide will be used in patients with AMI the present study was performed to evaluate the hemodynamic and antiarrhythmic effects of the drug and patient tolerance in this situation

Methods

Patients with AMI and frequent (more than five per minute) paired multifocal early premature ventricular contractions (PVCs) and/or ventricular tachycardia (runs of three or more PVCs rate over 100 beats/min) were studied within 24 hours of the onset of symptoms No antiarrhythmic agents other than tocainide were given before or during the study period Bedside catheterization was performed in the coronary care unit (CCU) and the right atrial pulmonary artery and aortic pressures were recorded continuously All pressures are given as means of at least five breathing cycles Cardiac output was determined by the thermodilution technique each value representing the mean of at least three consecutive measurements From the time of admission and during the whole CCU stay a continuous ECG was recorded and retained for visual evaluation

To provide an acute loading dose the first series of patients (Group 1) was given 0 [illegible] mg/kg/min tocainide as a continous infusion over 15 minutes The second series of patients (Group 2) received 0 75 mg/kg/min in the same way Hemodynamic measurements were performed immediately before as well as 15 30 45 and 60 minutes after the start of the tocainide infusion Thirty five minutes after termination of the infusion the patients randomly and double blindly received either two 400 mg tocainide tablets ([illegible] mg) or two placebo tablets Thereafter they received one tablet of either tocainide or placebo respectively every 8 hours for 24 hours Blood samples for tocainide analysis were collected from one of the catheters at 0 25 30 45 60 120 and 180 minutes after the start of the intravenous infusion as well as at 0 60 90 and 120 minutes

From the Department of Me[illegible] Institute at H[illegible]

Supported by a gr[illegible] Heart and Chest D[illegible]

Reprint requests O[illegible] [illegible] of Card[illegible]

[illegible] 131000 + [illegible] The C V Mosby Co

ell known[11] A total of 3 053 patients with myocardial infarction were studied 1 533 given practolol and 1 520 received a placebo duration of the study was 2 years There was erall reduction in the death rate including dden death rate of 38% The patients with ior myocardial infarction were reported to the most benefit although the reduction in n death rate was similar in the two groups ective of the site of the infarct

s study has been criticized on several ds such as it is not possible to assess the entativeness of patients with regard to or or inferior infarction without knowing mbers and reasons for exclusion from the and patients may have been selected as ed by the low total mortality rate The end of death and reinfarction were not clearly d if sudden death is the main end point it appear to be more important to discrimi ccording to blood pressure rather than to e of infarction Some workers have felt that sults presented did not warrant the conclu hat practolol is especially favorable in ts with a specific location of infarction Un able side effects from long term oral thera e now precluded the use of this agent

helmsson et al reported beneficial results prenolol in 230 patients subdivided into ent and placebo groups each stratified ne of four risk groups Group I had no ive cardiac damage Group II had mechan amage to the myocardium Group III had cal cardiac damage and Group IV was a nation of Groups II and III The dose of olol was 400 mg daily and the duration of al was 2 years Patients were entered 1 week hospital discharge After this time 11 ts in the placebo group and three in the ted group had died suddenly a small but cant fall in the sudden death rate resulted alprenolol therapy The mechanism of however is not clearly under —whether it is an antiarrhythmic effect or fect on myocardial metabolism Similar s have been reported by Ahlmark et al sing alprenolol The drug was given in a of 400 mg daily therapy being initiated 24 to 48 hours after the onset of infarction pected infarction The trial was continued year There was a significant reduction in ortality rate after 1 year in patients under 65 years of age There was no effect o th short term mortality rate It was not p ibl from the data presented to decide whether t e there was a significant drop in the sudden death rate although the results presented so ‹ (that practolol and alprenolol reduce the p farction mortality rate from sudden death

It is pertinent to ask whether the wide pr n use of beta blocker in all postmyocardial infarc tion patients is justified to achieve such a m ll percentage of benefit clinically If one assumes an annual postinfarction mortality rate of 6% and aims at achieving a 30% fall in the mortality rate with beta blocking therapy then only two out of every 100 patients would benefit Baber et al with the last point in mind carried out a long term trial in postinfarction patients using pro pranolol 40 mg daily designed on lines similar to the practolol trial their aim was to reduce the mortality rate by 50 c The trial failed to show a positive result

At present there are a number of long term trials being conducted throughout the world using various beta blockers such as acebutolol metoprolol oxprenolol pindolol propranolol sotalol and timolol (Table I) Whether these trials will answer certain questions posed by the practolol and alprenolol trials remains to be seen Certainly there has been no attempt in these trials to determine whether one beta blocker is superior to another Also none of these trials will define the mode of action of beta blockers in reducing the mortality rate Furthermore there does not appear to have been much attempt at stratifying patients to see what groups might benefit most from beta blocking therapy

Disopyramide

This drug has properties similar to those of quinidine and procainamide although its side effects are somewhat different because they are mainly confined to anticholinergic effects It has been shown to be as effective as quinidine in reducing ventricular ectopic activity but is claimed to have fewer side effects Comparative studies of disopyramide with atenolol mexilitine and placebo have been reported on a small num ber of patients but the duration of drug therapy was short 1 week for each drug No chronic comparative studies of disopyramide with other newer antiarrhythmic studies have been reported It is of interest however that Oshrain[1] has been

Table I Patient characteristics

Case No	*Sex*	*Age (yr)*	*Previous myocardial infarction*	*ECG site of infarction*	*S ASAT$_{max}$ (μkat/L)*	*Time from onset of symptoms to inclusion in study (hr)*	*Total amount of tocainide i.v. (mg)*	*Oral tocainide (T) or placebo (P)*
Group 1								
1	M	54	No	A L	6 05	12	550	T
2	M	58	No	S	0 82	12	533	P
3	M	66	Yes	I	1 08	16	575	T
4	M	65	No	A L	5 20	6	540	P
5	M	61	No	A	6 48	16	560	P
6	M	64	Yes	I L	5 36	20	525	P
7	F	73	No	S	3 40	9	585	P
8	F	71	No	A	1 16	12	526	T
9	M	68	Yes	A L	2 07	23	640	T
Group 2								
11	M	60	No	L	1 27	24	1 000	P
12	M	50	No	I	3 76	8	800	P
13	F	69	No	I	1 8	24	640	P
14	F	66	Yes	A	1 05	8	539	T
15	M	51	No	I L R	4 39	5	770	P
16	M	72	Yes	Uncertain	2 58	12	680	—
17	M	66	No	I	6 21	17	8 8	T
18	M	58	No	L,S	1 62	13	810	T
19	M	58	No	A	1 26	19	1 090	T

Abbreviations A = anterior L = lateral I = inferior S = subendocardial R = right ventricular S-ASAT$_{max}$ = maximal serum aspartate aminotransferase expressed in microkatals per liter

after the last oral dose at 24 hours Patients were questioned carefully to identify subjective symptoms and observed for objective signs of adverse effects The study code was broken after the hemodynamic antiarrhythmic and adverse effects had been evaluated in all patients

Results

Patient characteristics are shown in Table I There were no significant differences between Group 1 and Group 2 or between the tocainide and the placebo groups with respect to the variables described All patients were discharged from the hospital alive

Tocainide plasma concentrations Tocainide plasma concentrations for the two infusion rates are shown in Fig 1 At 15 minutes the mean plasma concentration for Group 1 patients receiving the 0 5 mg/kg/min dose was 43 8 ± 13 4 μmol/L For Group 2 patients receiving 0 75 mg/kg/min the 15 minute value was 63 6 ± 13 4 μmol/L The mean plasma concentration of the tocainide group at 24 hours immediately prior to the last oral dose was 26 6 ± 4 5 μmol/L

Hemodynamic measurements The mean and standard deviation of the hemodynamic measurements in all 18 patients are given in Table II At 15 minutes there was a small but significant increase in heart rate right atrial pressure pulmonary artery diastolic pressure aortic diastolic pressure and systemic vascular resistance There was also a small but significant decrease of cardiac index stroke index and left ventricular stroke work index Immediately before the tocainide infusion there were no statistically significant differences in any of the hemodynamic parameters between Group 1 and Group 2 patients At 15 30 45 and 60 minutes a significantly higher right atrial pressure was recorded in the Group 2 patients All other hemodynamic differences between the two groups were not statistically significant

The hemodynamic changes in the tocainide and placebo groups measured after the last oral dose at 24 hours are summarized in Tables III and IV At 0 minutes the time of the last dose there were no statistically significant differences between the tocainide and placebo groups with respect to

Table 1 Trials being conducted with beta blocking agents

Center	*Compound*	*No of patients*	*Prognostic stratification*
Multicenter France	Acebutolol	550	–
Stockholm Sweden	Metoprolol	250	+
Amsterdam Netherlands	Metoprolol	500	+
Gothenburg Sweden	Metoprolol	600	+
Multicenter USA	Metoprolol	3 000	–
Multicenter UK	Oxprenolol	1 100	–
Multicenter Germany	Oxprenolol	4 000	–
Multicenter Sweden Australia	Pindolol	500	–
Multicenter UK	Propranolol	[illegible]	–
Multicenter USA	Propranolol	4 200	–
Oslo Norway	Propranolol	500	–
Multicenter North England	Sotalol	1 600	–
Multicenter Norway	Timolol	1 800	+
Total		19 100	

reported to have used disopyramide therapy in 59 patients for 5 years with suppression of ventricular ectopic beats (VEBs) and ventricular tachycardia (VT) in 60% of cases without development of serious side effects Its effect in preventing ventricular fibrillation (VF) was not reported in this series Jenning et al claimed that disopyramide was effective in a controlled myocardial infarction (MI) study in reducing the mortality rate (VF) compared with placebo This study, however has been criticized on several grounds The number of patients studied was small (30 treatment versus 30 placebo) the mortality rate in the placebo group was relatively high the selection of patients for treatment or placebo group was not clearly defined a high percentage of patients in the 70 to 80 years of age group appear to have been included and some patients on disopyramide did not appear to have any drug detectable in their plasma

Furthermore in spite of claims that disopyramide is safer than quinidine serious side effects have been reported Ross et al[2] have demonstrated profound hypotension after a single dose and potent depressive effect on A V node/bundle of His conduction Podrid et al have concluded that disopyramide exerts a profound negative inotropic effect that is unique among antiarrhythmic agents manifesting itself as congestive cardiac failure (CCF) This appears during the first 3 weeks of therapy but may require several months to develop They suggest that disopyramide is not indicated in patients with [illegible] ly or a past history of CCF This study therefore casts a cautionary note over the long term use of disopyramide

In a short term comparative study recently completed by Hampton et al (personal communication 1980) involving oxprenolol disopyramide and placebo in acute infarct patients followed up for 6 weeks the results are of some interest in view of the preceding comment (1) There was no significant difference in mortality rates between the three agents (2) disopyramide reduced the incidence of ventricular ectopics without affecting the death rate and (3) there was an excess of heart failure in those patients treated with disopyramide confirming the experience of Podrid et al[2]

Mexiletine and tocainide

Mexiletine is one of the newer antiarrhythmic drugs tested in recent years In several studies it has been compared with procainamide atenolol disopyramide and tolamolol but mostly on a short term basis There is good evidence from other studies that it is effective against VEB and VT[3] While the short term studies indicate that it is at least as effective as procainamide and disopyramide and more effective than atenolol and tolamolol (against ventricular arrhythmias) it has rather frequent side effects What its relative merits are on a long term basis has not yet been shown

Two other antiarrhythmic agents have been used and compared with placebo in long term studies—aprindine and tocainide The former drug was studied by Hagemeijer et al[4] It involved

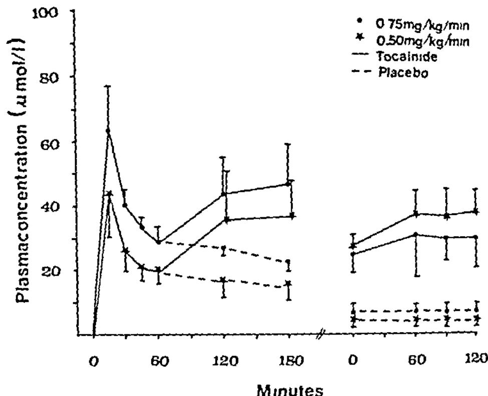


Fig 1 Tocainide plasma concentrations (± SD)

Table II Hemodynamic values in all 18 patients (mean and standard deviation)

Min	HR	RA	PA	PA	PA_m	AO	AO	AO_m	CI	SI	LVSWI	PVR	SVR
0	[illegible]	[illegible]	33±8	13±4	21±6	151±27	79±13	107±16	2.4±0.4	35±8	55±19	1.8±0.8	[illegible]
[illegible]	[illegible]	[illegible]	35±7	15±5	23±6	151±30	83±14	110±19	2.3±0.4	32±8	[illegible]	1.5±0.8	[illegible]
30	[illegible]	[illegible]	34±6	14±4	21±5	153±37	82±17	110±22	2.3±0.4	32±7	[illegible]	1.8±0.6	[illegible]
45	[illegible]	[illegible]	[illegible]	[illegible]	22±8	153±34	80±15	109±20	2.4±0.3	34±5	[illegible]	1.7±0.5	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	13±4	21±5	158±30	84±13	112±17	2.4±0.4	33±8	[illegible]	1.6±0.8	[illegible]

Abbreviation HR = heart rate (beats/min) RA = mean right atrial pressure (mm Hg) PA = pulmonary artery pressure (mm Hg) AO = [illegible] pressure (mm Hg) CI = cardiac index [illegible] SI = stroke index [illegible] LVSWI = left ventricular stroke work index [illegible] PVR = pulmonary vascular resistance (resistance units) SVR = systemic resistance (resistance units)

[illegible]

any of the hemodynamic parameters In the tocainide group there was a small but statistically significant rise in the mean aortic pressure from 102 mm Hg at 0 minutes to 105 mm Hg at 90 minutes ($P < 0.05$) No other significant hemodynamic changes were observed In the placebo group there was an increase of heart rate from 81 beats/min at 0 minutes to [illegible] beats/min at 45 minutes (P [illegible]) and to [illegible] beats/min at 90 minutes ($P < 0.01$) The mean [illegible] pressure fell significantly from [illegible] mm Hg [illegible] minutes to 91 mm Hg at 90 minutes ([illegible]) No other significant hemodynamic [illegible] observed in this group No significant differences between the tocainide and the placebo groups were observed at 0 45 60 and 90 minutes with respect to any of the hemodynamic parameters

Antiarrhythmic effects Seven patients had ventricular tachycardia within 1 hour prior to the tocainide infusion compared to one patient during the 1 hour after the start of the infusion ($P < 0.05$) The corresponding figures for multifocal PVCs were nine and two patients respectively ($P < 0.05$) and for paired PVCs nine and three patients respectively ($P < 0.05$)

Within the nearest 15 minutes prior to the start

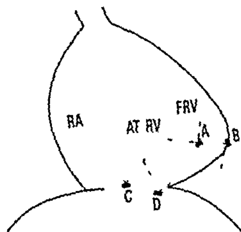


Fig 1 Position of the transducer and direction of the ultrasonic beam Position *A* provides an apical four-chamber view and position *B* shows a three chamber view of the right-sided heart from the apex which is nearly perpendicular to the cross section for the apical four chamber view Position *C* provides a horizontal subxiphoid cross-section and *D* indicates subxiphoid cross-section along the left costal margin

the STL in 10 normal subjects and in 10 patients with ASD of secundum type

b Three chamber view An apical three chamber view was obtained in nine of the 11 patients Fig 4 shows an example of the three chamber view in the same patient as Fig 2 A remarkable displacement of the STL is visualized whereas the ATL attaches to the original valve ring Moreover the tricuspid valve ring *(TVR)* is clearly visualized

Additionally the chordae tendineae inserting into the ATL were visualized in four instances from the four chamber view and in five cases from the three chamber view respectively

2 Subxiphoid cross-section We succeeded in recording the subxiphoid cross section in nine out of the 11 patients whereas in the remaining two the interpretable images could not be obtained due to liver enlargement or tight abdominal wall In order to obtain better images from this area we adjusted the gain setting by increasing the intensity of the ultrasonic beam and deepened the focal point

As a result the right sided heart chambers were widely observed as well as the interventricular septum and the left ventricle Moreover the elongated ATL was demonstrated clearly from the tip to the root attached to the tricuspid valve ring in eight out of the nine patients In addition the root of the ATL was remarkably thickened in five Fig 5 shows a subxiphoid cross section taken

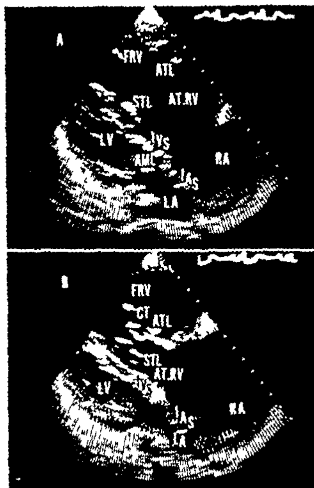


Fig 2 Four chamber view by cross section through the apex in a 3-year-old patient with Ebstein's anomaly *Top* diastolic picture *Bottom* systolic image The septal tricuspid leaflet is displaced downward into the right ventricle resulting in the formation of the atrialized and functional right ventricles *FRV* = functional right ventricle *AT RV* = atrialized right ventricle *RA* = right atrium *STL* = septal tricuspid leaflet *ATL* = anterior tricuspid leaflet IVS = interventricular septum IAS = interatrial septum *AML* = anterior mitral leaflet *LV* = left ventricle *LA* = left atrium *CT* = chordae tendineae

from the same patient as shown in Fig 2 The ATL is fully visualized from the tip to the root attached to the tricuspid valve ring The chordae tendineae *(CT)* inserting into the ATL are also discernible Fig 6 shows another example of the subxiphoid cross section in a 5 year old patient (F A) The ATL was fully described from the tip to the thickened root well as a part of the interventricular septum and the left ventricle In six patients the CT to the ATL was visualized in the subxiphoid cross section Moreover a hypertrophied anterolateral papillary muscle was also recognized in the subxiphoid cross section in one instance

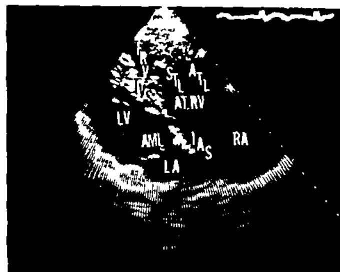


Fig 3 Another example of the four chamber view in a 21 year old female (A I) with Ebstein's anomaly and PFO The STL is displaced into the right ventricular cavity Abbreviations are the same as in *Fig 2*



Fig 5 Subxiphoid cross section taken from the same patient as in *Fig 2* The ATL is fully visualized from the tip to the root anchored on the right atrioventricular junction. The chordae tendineae *(CT)* inserting into the ATL are also discernible *CT* = chordae tendineae other abbreviations are the same as in *Fig 2*

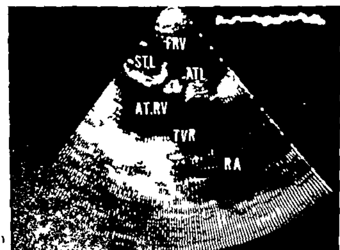


Fig 4 Three chamber view of the right sided heart by cross section through the apex in the same patient as in *Fig 2* The functional and atrialized right ventricles and the right atrium were depicted by cross section through the cardiac apex in direction *B* as shown in *Fig 1* Abbreviations are the same as in *Fig 2*

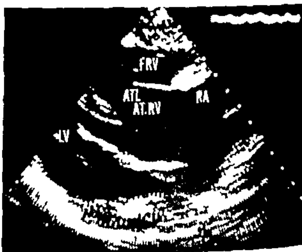


Fig 6 Another example of the subxiphoid cross section obtained from a 6 year old patient (F A) with Ebstein's anomaly associated with patent foramen ovale The elongated ATL is fully seen from the tip to the thickened root and the right side of the heart is widely visualized Abbreviations are the same as in *Fig 2*

In three patients the STL was found to be displaced downward by the subxiphoid approach

Discussion

Recently cross sectional echocardiography has come into clinical use thus providing useful information on cardiac anatomy and movements It is suitable for the spatial orientation of the heart structures because of its two dimensional nature

Matsumoto and associates[16] reported on the visualization of the tricuspid valve in Ebstein's anomaly using a mechanical sector scan However the probe was too large to be easily manipulated and the apical and subxiphoid approaches were not available Hirschklau and associates[7] applied a multicrystal echocardiographic system to this lesion to obtain real time observation of the tricuspid valve abnormalities However the scanner was not appropriate for the cross section through the subxiphoid area and the problem of

Table III *Hemodynamic changes in the tocainide group at the time of the last dose (mean and standard deviation)*

Min	HR	RA	PA	PA	PA_m	AO	AO	AO	CI	SI	LVSWI	PVR	SVR
0	84 ± 18	4 ± 2	33 ± 13	14 ± 6	23 ± 10	139 ± 25	76 ± 14	102 ± 17	2.6 ± 0.5	31 ± 2	45 ± 8	1.8 ± 0.9	[illegible]
45	83 ± 19	4 ± 2	33 ± 11	14 ± 7	22 ± 10	14[illegible] ± 29	80 ± 16	105 ± 17	2.6 ± 0.3	32 ± 5	48 ± 12	1.9 ± 1.0	21.3 ± 4.8
60	84 ± 17	4 ± 2	32 ± 12	14 ± 6	21 ± 11	141 ± 27	78 ± 13	104 ± 17	2.6 ± 0.3	32 ± 4	49 ± 9	1.8 ± 1.3	20.9 ± 5.2
90	84 ± 18	4 ± 3	37 ± 11	13 ± 8	22 ± 12	143 ± 20	79 ± 14	105 ± 1	2.6 ± 0.3	32 ± 5	47 ± 12	1.8 ± 0.6	20.3 ± 4.4

For abbreviations, see Table II
$P < 0.0$

Table IV Hemodynamic changes in the placebo group at the time of the last dose (mean and standard deviation)

Min	HR	RA	PA	PA	PA_m	AO	AO	AO_m	CI	SI	LVSWI	PVR	SVR
0	81 ± 5	4 ± 4	[illegible]8 ± 13	10 ± 6	18 ± 6	130 ± 17	74 ± 11	99 ± 12	2.7 ± 0.4	34 ± 6	49 ± 14	1.6 ± 0.7	18.8 ± 1.2
45	85 ± 6	4 ± 4	29 ± 13	9 ± 4	17 ± 6	127 ± 16	[illegible]2 ± 12	95 ± 11	2.7 ± 0.4	32 ± 5	45 ± 14	1.6 ± 0.7	18.7 ± 1.5
60	80 ± 7	4 ± 4	28 ± 13	9 ± 4	16 ± 6	12[illegible] ± 15	72 ± 10	94 ± 10	2.7 ± 0.3	32 ± 4	44 ± 10	1.6 ± 0.7	18.3 ± 1.8
90	86 ± [illegible]†	4 ± 4	27 ± 12	9 ± 4	16 ± 6	126 ± 15	[illegible]7 ± 11	94 ± 10	2.[illegible] ± 0.3	32 ± 5	43 ± 12	1.5 ± 0.7	17.8 ± [illegible]

For abbreviations, see Table II
*$P < 0.05$
†$P < 0.01$

of the tocainide infusion four patients had more than five PVCs per minute. A reduction of the number of PVCs was seen in all four patients during 60 minutes following the start of the infusion. There were no statistically significant differences between the tocainide and placebo groups during the tablet administration period with respect to the incidence of ventricular tachycardia, multifocal PVCs, or paired PVCs. The number of PVCs in the tocainide group was significantly higher than the number in the placebo group during both the pretreatment period ($P < 0.01$) and the treatment period ($P < 0.001$). One patient in the placebo group (Case 7) developed ventricular fibrillation 4 hours after the start of the tocainide infusion (plasma concentration at this time 18.7 µmol/L).

Adverse effects. In association with the intravenous infusio[illegible] six patients, three in each group, had no adver[illegible] [illegible]cts at all. Eight patients, four in each grou[illegible] [illegible]rted a cool throat and a fresh taste of [illegible] mint, which was described as pleasant o[illegible] [illegible]npleasant, between 5 and 10 (mean 8 ± [illegible] after the start of the infusion. The d[illegible] [illegible]ned between 4 and 30 (mean 13 ± 8) m[illegible] [illegible] correlation was found between plasma [illegible] [illegible]ion of tocainide and side effects. Two p[illegible] [illegible]orted lightheadedness and two had on[illegible] [illegible] ode of vomiting 35 minutes after the start of the infusion. Three patients (Cases 3, 16, and 19) had bradycardia and hypotension 20, 25, and 35 minutes after the start of the tocainide infusion. They were easily treated by a head-down posture in two patients and atropine in the third patient with prompt disappearance of symptoms. No significant differences between the tocainide and placebo groups were observed during the long-term tablet administration period with respect to adverse effects (Table V).

Table V Adverse effects during the tocainide/placebo tablet period

Adverse effects	*Tocainide group*	*Placebo group*
No adverse effects	5	5
Nausea	1	1
Vomiting	1	2
Generalized warmth	0	1
Bradycardia and hypotension	1	0

Discussion

The new antiarrhythmic drug tocainide is effective against ventricular tachyarrhythmias when given both intravenously and orally. The effect seems to correlate with the concentration of drug in the plasma and a therapeutic range of 18 to 45

Tocainide for refractory ventricular arrhythmias of myocardial infarction

Charles I Haffajee M B Joseph S Alpert M D and James E Dalen M D *Worcester Mass*

Oral tocainide was used as a long term antiarrhythmic in patients with symptomatic high-grade ventricular ectopic activity refractory to conventional antiarrhythmic agents Eleven of the 22 patients had a previous myocardial infarction (three patients had a ventricular aneurysm) Unacceptable side effects precluded long term use of tocainide in two patients Long term tocainide was effective in six of the remaining patients for periods of 9 days to 42 5 months (mean 15 2 months) Eight of these nine patients responded to intravenous lidocaine prior to tocainide therapy

Chronic antiarrhythmic therapy with tocainide was evaluated in 22 patients with symptomatic high grade ventricular ectopic activity (10 with life threatening ventricular tachycardia) resulting from a variety of cardiac diseases The arrhythmias were refractory to all currently available antiarrhythmic agents in the United States both singly and in combination Eleven of the 22 patients had a previous myocardial infarction Unacceptable side effects precluded use of tocainide in two patients hence the experience in the remaining nine patients with previous cardiac infarction forms the basis of this report

Material and methods

Twenty two patients with refractory symptomatic high grade ventricular ectopic activity (VEA) including 10 patients with symptomatic ventricular tachycardia (VT) were considered for tocainide therapy Eleven of the 22 patients had a previous myocardial infarction and long term experience with nine of these patients forms the basis of this report (Table I) Three of these nine patients had a documented ventricular aneurysm and six of the nine patients had VT The ages of the nine patients ranged from 28 to 42 years (mean 54 years) eight patients were male Tocainide was employed chronically in these nine patients for 0 3 to 42 5 months (mean 25 5 months)

All nine patients had been previously treated with conventional antiarrhythmic agents available in the United States In the majority of the patients adequate plasma levels of these agents were achieved before their lack of efficacy was accepted The drugs were used singly and in combination or were considered to be contraindicated before tocainide therapy was instituted Of the agents used (Table II) quinidine was ineffective in all nine patients Procainamide was used in seven patients and found to be ineffective in five produced lupus erythematosus in two and was contraindicated in one patient Disopyramide was ineffective in two of the five patients in whom it was used and had to be discontinued because of unacceptable side effects in the remaining three (60%) patients Disopyramide was contraindicated in three patients and not commercially available for use in one patient Propranolol was ineffective in five of the nine patients in whom it could be used

Oral tocainide was begun after discontinuation of all previous antiarrhythmic agents with the exception of lidocaine It was initially employed at 400 mg every 6 to 8 hours and more recently at a dose of 600 mg every 8 to 12 hours The dosage was increased every 24 to 48 hours until acceptable arrhythmia control or unacceptable side

From the Department of Medicine Division of Cardiovascular Medicine University of Massachusetts Medical School Worcester Mass.

Reprint requests Charles I. Haffajee M D Assistant Professor of Medicine Director of MICU-CCU Division of Cardiovascular Medicine University of Massachusetts 55 Lake Ave North, Worcester MA 01605

0002 8 03/80/131013 + 04$00 40/0 © 1980 The C V Mosby Co

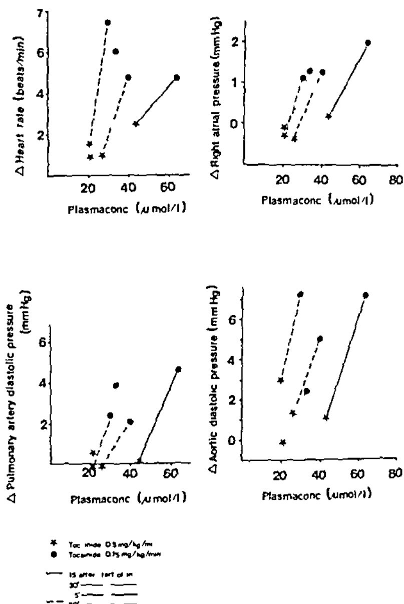


Fig 2 Changes in heart rate right atrial mean pressure pulmonary artery diastolic pressure and aortic diastolic pressure in relation to plasma concentration of tocainide and two infusion rates

μmol/L has been suggested In the present study only one of the Group 1 patients was slightly below the recommended therapeutic interval during the 45 minutes after the tocainide infusion On the other hand five of the Group 2 patients had plasma concentrations rather high above the suggested therapeutic range at 15 minutes after the start of the infusion Until the therapeutic range has been definitely settled the data from the present investigation suggest that an infusion rate of 0 ,0 mg/kg/min may be sufficient in patients with AMI Plasma conc ... trations were well within the suggested therap ... range with the dosage regimen of ... followed by 400 mg t i d used in the ...

The patients participating in the present study all had AMI with onset of symptoms with n 24 hours prior to the tocainide infusion Some of the patients had considerable left ventricular dysfunction cardiac indices varying between 1 7 and 3 1 L/min/m² pulmonary artery diastolic pressures varying between 4 and 20 mm Hg and/or right ventricular failure with mean right atrial pressures varying between 0 and 11 mm Hg Intravenous tocainide was well tolerated hemodynamically by all patients but three Although statistically significant the hemodynamic changes were small In all 18 patients the mean change at 15 minutes was an increase in heart rate of 3 beats/min (4%) in mean right atrial

Table I Summary of patients on long term tocainide therapy

Sex	Age	VA	Duration of therapy (mo)	Tocainide dose (mg/day)	Dosing interval (hr)	ET induced before tocainide	VEA during tocainide	VT		Lown grade	
								Before tocainide	During tocainide	Before tocainide	During tocainide
M	63	No	12	1,800	8	No	—	No	No	4A	3
M	[illegible]	No	32	1,800	8	—	—	Yes	No	4B	1
M	[illegible]	—	9	1,800	8	No	No	No	No	4B	4A
M	41	No	23	1,200	8	No	No	No	No	4B	2
M	66	Yes	0.3	2,400	8	Yes	Yes	Yes	Yes	4B	4B
M	44	Yes	42.5	3,[illegible]00	6	No	No	Yes	No	4B	3
M	[illegible]	No	2	1,200	8	—	—	No	No	4A	1
F	[illegible]	Yes	0.3	1,800	8	—	—	Yes	Yes	4B	4B
M	[illegible]8	No	3.5	1,800	8	Yes	No	Yes	No	4B	1

Abbreviations VA = ventricular aneurysm ET = treadmill exercise testing VEA = ventricular ectopic activity VT = ventricular tachycardia

Table II Treatment before tocainide

Drug	No of patients	Not effective	Contraindicated	Side effects
Quinidine	9	9	0	2
Procainamide	[illegible]	5	1	2
Disopyramide	5	2	3	3
Propranolol	5	[illegible]	4	0
Phenytoin	3	3	0	0

effects intervened After 48 hours of therapy an absorption distribution tocainide curve was obtained in every patient and thereafter trough levels were used as a guide to therapeutic effectiveness Peak levels which are achieved 60 to 90 minutes after the drug is taken were obtained if side effects occurred The daily tocainide dose ranged from 1,200 to 3 200 mg/day (mean 1 900 mg/day) in the nine patients

Prior to oral tocainide therapy ventricular arrhythmias in all nine patients were documented during ambulatory coronary care unit or telemetry ECG monitoring. Subsequent short term (computerized arrhythmia detection system) and long term ECG ambulatory (Holter) monitoring was conducted at frequent intervals during tocainide therapy In addition treadmill exercise testing (Bruce protocol) was employed in two patients in whom exercise testing had induced VEA/VT

Ventricular arrhythmias were assessed by hourly counts of VEA and occurrence of couplets and VT during frequent outpatient ambulatory ECG monitoring A reduction in VEA and elimination of couplets and/or VT was sought during treadmill exercise testing in the two patients with exercise induced VEA/VT

Symptoms caused by VEA/VT were also monitored in all patients during oral tocainide therapy Side effects were monitored through spontaneous comments and direct questioning at each visit Prior to institution of tocainide therapy baseline ECGs chest x ray films antinuclear antibody (ANA) titers Coombs test and hematologic hepatic and renal function were assessed In addition urinalysis and ophthalmologic assessment were performed on all the patients At periodic intervals throughout the duration of therapy these tests were repeated

Results

Results are shown in Table I

Arrhythmias In three of five patients with VT there was either abolition or marked reduction in episodes of VT while they were on tocainide as assessed by 24 hour ambulatory monitoring (two patients) and by exercise testing (one patient)

In five of the nine patients there was a significant reduction in total hourly VEA count ([illegible] VEA/hr before and 44 VEA/hr during tocainide therapy $P < 0.05$ Student's t test) However in the group as a whole the mean hourly VEA before tocainide therapy was 362 ± 347 whereas during tocainide therapy it was 9[illegible] ± [illegible] ($P = 0.08$ Student's t test) In one patient there was an increase in mean hourly VEA count (13 to 60) When the Lown system of grading VEA was used for analysis there was an improvement in Lown grade of VEA in six of the nine patients All nine patients were in Lown grade 4A or 4B prior to tocainide therapy Three patients improved

pressure of 1 mm Hg (25%) in pulmonary artery diastolic pressure of 2 mm Hg (19%) in aortic diastolic pressure of 4 mm Hg (5%) and in systemic vascular resistance of 2 units (10%), there was a decrease in cardiac index of 0 2 L/min/m² (6%) and in stroke index of 3 ml/m At 30 and 45 minutes there was a gradual return toward control values Although correlated to the tocainide plasma concentrations the hemodynamic changes seemed to be more dependent upon the tocainide infusion rate as shown in Fig 2 During the tablet administration period no significant differences were observed at any time between the tocainide and placebo groups with respect to any of the hemodynamic variables measured

Although some of the arrhythmias in the present study may have been artificially caused by the catheters a significant antiarrhythmic effect was seen during 1 hour after the tocainide infusion regarding ventricular tachycardia and multifocal and paired PVCs In the four patients who had more than five PVCs per minute a reduction of the number of PVCs was seen in all During the tocainide/placebo tablet period no significant difference was observed between the tocainide and placebo groups with respect to the incidence of ventricular arrhythmias Most patients had minor side effects of little clinical importance However three patients after the infusion had sudden onset of bradycardia and hypotension which were easily and rapidly treated

Summary

The hemodynamic and antiarrhythmic effects were evaluated after tocainide was given intravenously over a 15 minute period to 18 patients with AMI within 24 hours after onset of symptoms Doses were 0 5 (nine patients) and 0 75 (nine patients) mg/kg/min Tocainide infusion produced small but statistically significant increases in heart rate mean right atrial pressure pulmonary artery diastolic pressure aortic diastolic pressure and systemic vascular resistance It also caused small but significant decreases in cardiac index stroke index and left ventricular stroke index Although correlated to the tocainide plasma concentrations the hemodynamic changes seemed to be more dependent upon the tocainide infusion rate The data from the present investigation suggest that an infusion rate of 0 50 mg/kg/min may be sufficient in patients with AMI Ventricular tachycardia and multifocal and paired PVCs were significantly reduced after tocainide infusion Most patients had side effects but these were mild and transient After the tocainide infusion however three patients had an episode of bradycardia and hypotension which were easily and rapidly treated in all patients

After the infusion the patients randomly and double blindly received either two 400 mg tocainide tablets or two placebo tablets and thereafter one tablet of either tocainide or placebo respectively every 8 hours for 24 hours This resulted in plasma concentrations within the suggested therapeutic range no significant hemodynamic changes and minor side effects These findings suggest that oral tocainide can be used safely for antiarrhythmic therapy in patients with AMI

REFERENCES

1 Coltart DJ Berndt TB Kernoff R Harrison DC Antiarrhythmic and circulatory effects of Astra W 36095 A new lidocaine-like agent Am J Cardiol **34** 35 1974
2. Winkle RA Anderson JL, Peters F Meffin PJ Fowles RE Harrison DC The hemodynamic effects of intravenous tocainide in patients with heart disease Circulation **57** 787 1978
3 Engler R Ryan W LeWinter M Bluestein H Karliner JS Assessment of long term antiarrhythmic therapy Studies on the long term efficacy and toxicity of tocainide Am J Cardiol **43** 61[illegible] 1979
4 Woosley RL, McDevitt DG Nies AS Smith RF Wilkinson GR Oates JA Suppression of ventricular ectopic depolarizations by tocainide Circulation **56** 980 1977
5 Winkle RA Meffin PJ Fitzgerald JW Harrison DC Clinical efficacy and pharmacokinetics of a new orally effective antiarrhythmic tocainide Circulation **54** 884 1976

from Grade 4 to 1 two patients from Grade 4 to 3 and one patient from Grade 4 to 2 (Table I Fig 1) Three of five patients noted considerable improvement in palpitations

Pharmacokinetics The peak plasma tocainide levels in the nine patients ranged from 8 7 to 15 1 μg/ml (mean 10 6 μg/ml) The trough tocainide levels ranged from 1 4 to 7 5 μg/ml (mean 5 0 μg/ml) Higher trough (6 7 versus 4 0 μg/ml) and peak (12 7 versus 9 4 μg/ml) levels of tocainide were achieved in nonresponders compared to responders

Side effects Transient central nervous system (CNS) symptoms occurred in seven of the nine patients (77%) at some early point during tocainide therapy The most common symptoms were paresthesias (3 patients) ataxia (4 patients) blurring of vision (2 patients) and slurred speech (4 patients) Severe CNS side effects occurred in two patients on day 1 and day 3 of therapy (confusion and paranoia in one patient ataxia of gait and speech in the other) and precluded long term use of tocainide in these patients

Minor gastrointestinal side effects (nausea anorexia and vomiting) occurred transiently in six of the nine patients However both the gastrointestinal and CNS side effects were overcome in all nine patients by reduction of dosage or taking the drug with food

ANA titers were slightly elevated in three patients during tocainide therapy In one patient who previously developed procainamide induced lupus the ANA titers were markedly elevated prior to tocainide therapy In this individual ANA titers fell during tocainide therapy In two other patients minimally elevated ANA titers developed during long term tocainide therapy However neither of these patients has developed clinical evidence of lupus as yet The patient with procainamide induced lupus developed a skin rash on chronic tocainide therapy that did not recur on reinstitution of tocainide after initial withdrawal

No systemic (hepatic renal hematologic and ophthalmologic) abnormalities were detected during periodic blood tests during chronic tocainide therapy No significant ECG conduction abnormalities were detected during chronic tocainide therapy

Intravenous lidocaine responsiveness in the prediction of tocainide efficacy Intravenous lidocaine was used in eight of the nine patients for suppression of VT/VEA prior to tocainide therapy Long term oral tocainide was effective in six of the eight lidocaine responders (75%)

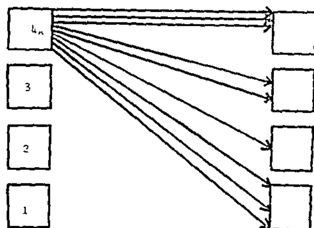


Fig 1 Improvement in Lown grade during tocainide therapy

Patients dying while on long term tocainide therapy Two patients died while on chronic tocainide therapy One of the two patients died from refractory cardiac failure 21 days following an extensive myocardial infarction and the second patient died from chronic congestive cardiac failure Neither of these deaths appeared to be related to tocainide therapy

Withdrawal of tocainide therapy Tocainide withdrawal was attempted in two responders after 28 and 19 months of chronic therapy respectively In both patients there was a prompt return of VEA during ambulatory monitoring in the first month following discontinuation of therapy No withdrawal was attempted in the three patients with VT who responded to and were on long term tocainide therapy

Discussion

Tocainide was effective in six of the nine (66%) patients for periods from 9 days to 42 5 months (mean 15 2 months) Four (41%) of these patients are still on maintenance tocainide therapy for periods of 3 5 to 42 5 months (mean 25 5 months) Three of the nine patients had a ventricular aneurysm and tocainide was effective in only one of these three patients In the majority of patients the drug was given every 8 hours and dosages ranged from 1,200 to 3 200 mg/day (mean 1,900 mg/day)

Minor side effects early on in therapy were

Prophylaxis of ventricular tachyarrhythmias with intravenous and oral tocainide in patients with and recovering from acute myocardial infarction

Lars Rydén, M.D., Krister Arnman, M.D., Thor Bjorn Conradson, M.D., Stefan Hofvendahl, M.D., Ole Mortensen, M.D., and Peter Smedgard, M.D.
Skövde and Helsingborg, Sweden

In a double-blind placebo controlled study, tocainide 750 mg i.v. during a 15 minute period directly followed by 800 mg orally and later 400 mg t.i.d. was administered to patients with acute myocardial infarction (AMI). Treatment was started as soon as possible following onset of symptoms; the follow-up period was 6 months. The patient groups consisted of 56 tocainide and 56 placebo patients. There was no significant effect on the incidence of ventricular fibrillation or symptomatic ventricular tachycardia. The mortality rates were similar and low in both groups. Tocainide suppressed ventricular arrhythmias including ventricular tachycardia, both in the acute stage of AMI and during convalescence. Tocainide also suppressed exercise induced ventricular arrhythmias. Side effects were in general mild or moderate.

Tocainide is an important new membrane active antiarrhythmic agent which we have evaluated in patients after myocardial infarction. The primary aim of this study was to assess the ability of tocainide to prevent ventricular fibrillation (VF), symptomatic ventricular tachycardia (VT), and sudden death in patients with acute myocardial infarction (AMI). Secondary aims were to assess the activity of tocainide against less serious spontaneous and exercise induced arrhythmias such as short runs of VT and ventricular premature complexes (VPCs) and to study the safety of intravenous and oral tocainide when given to patients with and recovering from AMI.

Material and methods

Patients. The patients enrolled in the study were all admitted to the coronary care units (CCUs) of the Central Hospitals of Skövde and Helsingborg, Sweden, during the period from June 1978 to May 1979. All patients less than 71 years old admitted with symptoms suggestive of AMI within the previous 48 hours were considered for inclusion. Indications for exclusion are summarized in Fig. 1.

Patients suitable for inclusion were then randomly treated with either tocainide or matching placebo. The dose of tocainide was 750 mg i.v. given by continuous infusion over a 15 minute period, 800 mg orally given at the end of the infusion, and 400 mg orally given every 8 hours starting 8 hours later. Patients in the placebo group received intravenous saline solution followed by lactose tablets in an identical regimen. Treatment with oral medication was then continued double blind for a period of 6 months after the initial admission. Patients were withdrawn from the study if the diagnosis of AMI was not confirmed or if they developed defined exclusion criteria (Fig. 1).

Assessment procedures. All patients included in the study were subject to standard CCU surveillance and treatment, and following discharge they were assessed clinically at 1, 3, and 6 months.

Continous ECG recordings were made by means of an Oxford instrument recorder for the first 24 hours in the hospital, on day 10 (before discharge) and at Skövde 1 and 6 months after

From the Department of Me[illegible] Sk[illegible]de and H[illegible]singborg, Sweden.
Reprint requests: La[illegible] M.D., Me[illegible] Hospital, [illegible]

[illegible]8703/80/1310[illegible] + 0[illegible] 0 [illegible] 1980 The C. V. Mosby Co.

experienced by the majority of patients (9 of 12 75%) However side effects were transient and overcome gradually by taking the drug with food or by dosage reduction Side effects precluded long term therapy with tocainide in 2 of the 11 (18%) patients

Intravenous lidocaine was effective in eight of the nine patients with myocardial infarction Oral tocainide subsequently proved to be effective long term in six (75%) of these lidocaine responders

No adverse conduction abnormalities were detected during this study However none of the patients underwent intracardiac electrophysiology before or during tocainide therapy Moore et al[2] have characterized the electrophysiologic safety of tocainide in man

The effectiveness of tocainide in suppressing VEA VT in man has previously been demonstrated in short term studies by Winkle et al [3] Woosley et al and Ryan et al [5] and in long term studies by Winkle et al [6] and Engler et al [7] However in both of these long term studies [7] disopyramide was not employed prior to tocainide therapy Moreover other antiarrhythmic medications were continued in their patients while on tocainide therapy

We recognize the limitations of 24 hour and short term ambulatory ECG monitoring [8] the Lown grading system the lack of a single accurate and reproducible standard for monitoring arrhythmias and the lack of intracardiac VT initiation by pacing during tocainide therapy in our patients However it appeared that in our highly symptomatic group of patients with VEA/VT resulting from chronic coronary artery disease both symptomatic episodes of VT and VEA counts and complex forms decreased during tocainide therapy

Tocainide appears to be a promising and useful addition to our limited armamentarium of antiarrhythmic agents It would appear to be a logical choice for chronic therapy in those patients in whom lidocaine results in VEA/VT suppression An acceptable level of side effects was noted early in therapy and no long term sequelae resulted from tocainide therapy in our patients

REFERENCES

1 Lown B Graboys TB Management of patients with malignant ventricular arrhythmias Am J Cardiol 39 910 1977
2 Moore EN Spear JF Horowitz LN Feldman HS Miller RA Electrophysiologic properties of a new antiarrhythmic drug—tocainide Am J Cardiol 41 703 1978
3 Winkle RA Meffin PJ Fitzgerald JW Harrison DC Clinical efficacy and pharmacokinetics of a new orally effective antiarrhythmic tocainide Circulation 54 884 1976
4 Woosley RL, McDevitt DG Nies AS Smith RF Wilkinson GR Oates JA Suppression of ventricular ectopic depolarizations by tocainide Circulation 56 980 1977
5 Ryan W Engler R LeWinter M Karliner JS Efficacy of a new oral agent (tocainide) in the acute treatment of refractory ventricular arrhythmias Am J Cardiol 43 [illegible] 1979
6 Winkle RA Meffin PJ Harrison DC Long term tocainide therapy for ventricular arrhythmias Circulation 57 1008 1978
7 Engler R Ryan W LeWinter M Bluestein H Karliner J Assessment of long term antiarrhythmic therapy Studies on the long term efficacy and toxicity of tocainide Am J Cardiol 43 612 1979
8 Morganroth J Michelson EL, Horowitz LN Josephson MF Pearlman AS Dunkman WB Limitations of routine long term electrocardiographic monitoring to assess ventricular ectopic frequency Circulation 58 408 1978
9 Bigger JT Wenger TL, Heissenbuttel RH Limitations of the Lown grading system for the study of human ventricular arrhythmias Am Heart J 93 727 1977

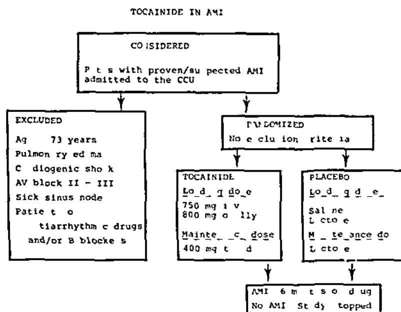


Fig 1 Study design

discharge The patients from Skovde also had ECGs recorded during exercise testing on a bicy cle ergometer conducted 1 3 and 6 months after discharge

Exercise tests were performed on an electrically braked bicycle ergometer (Siemens Elema Swe den) under standardized conditions The ECG was recorded at each work load reached and repeatedly during the first 10 minutes after exer cise The initial work load was usually 30 watts for women and 50 watts for men which was then increased stepwise by 10 watts/min For the exercise test 1 month following AMI patients exercised either until definite symptoms occurred or until the increase in heart rate or other obser vations was such that it was thought prudent to stop For the exercise tests at 3 and 6 months all patients were exercised until symptoms such as angina pectoris dyspnea and tiredness made it impossible to continue work serious ventricular tachyarrhythmias occurred (VT or numerous VPCs with hemodynamic deterioration) or a combination of these problems was noted Thus the work load at 3 and 6 months may be consid ered maximal

All 24 hour tapes were analyzed both by the use of a Pathfinder Arrhythmia Computer and by eye following operator controlled printout of sus picious events The number of hours containing no arrhythmias infrequent (< 30/hr) or frequent (> 30/hr) VPCs or VT (rate > 100 three or more consecutive beats) and the number of patients with these arrhythmias in any assess ment period was used for comparisons between the groups

Exercise induced ventricular tachyarrhyth mias reported are arrhythmias occurring either during or directly following the exercise test and disappearing spontaneously with continued rest

These VPCs have been classified as monofocal multifocal and paired and their frequency esti mated at the time of occurrence

Results

A total of 162 patients who fulfilled entry criteria were enrolled in the study One other patient entered 55 hours after the onset of symp toms was excluded from the overall analysis One hundred and twelve patients were diagnosed as having AMI by WHO criteria and of these 56 were given tocainide and 56 placebo In 50 patients the diagnosis of AMI could not be sus tained Twenty six of these patients received tocainide and 24 placebo

Because of technical difficulties it was not possible to analyze the tape recordings made in one of the centers (Helsingborg) Spontaneous ventricular arrhythmias not resulting in with drawal from the study therefore are reported only for the patients enrolled at Skovde Technical problems resulted in the loss of only a few tapes (~ 6%) and full 24 hour recordings were obtained

III Chronic tocainide therapy studies

A prospective randomized trial of tocainide in patients following myocardial infarction

B C Bastian M B Ch B, P W Macfarlane B Sc Ph D J H McLauchlan M B Ch B D Ballantyne, M D R Clark M B Ch B W S Hillis M B Ch B A P Rae B Sc M B and I Hutton M D *Glasgow, Scotland*

One hundred forty six patients with recent acute myocardial infarction were grouped at random into those treated with tocainide an oral analogue of lignocaine or placebo and followed up for 6 months In addition to standard investigations a 24-hour ambulatory taped ECG recording was obtained prior to randomization and thereafter at 2 8 16 and 24 hours after discharge The ECGs were analyzed by means of an automated computerized reporting system Forty two patients had significant ventricular arrhythmias 10 of whom had effective plasma levels of tocainide compared with 27 patients on placebo ($P < 0.005$) In the placebo patients with increasing mobilization there was a consistent rise in the number of ventricular ectopic beats per day There was no such increase in the tocainide patients ($P < 0.01$) Side effects were few and the incidence of central nervous system side effects was similar in both the tocainide and placebo groups There was no conclusive evidence of myocardial depression heart rate and blood pressure being unchanged over the 6 month period Although ventricular arrhythmias were suppressed the number of patients in the study was too small to draw conclusions regarding the mortality rate

The risk of sudden death is increased in patients with coronary heart disease particularly in patients with ventricular ectopic beats[1-4] It therefore seems reasonable to try and prevent such ventricular arrhythmias Tocainide is an analogue of lignocaine and has been shown to be an effective antiarrhythmic agent in animals and in several preliminary studies in patients It is almost 100% absorbed after oral administration and has a plasma half life of approximately 12 hours in patients with normal renal and hepatic function[11,12] The purpose of the present study was to evaluate the effects of tocainide on the prevention of ventricular arrhythmias in a placebo controlled trial in patients recovering from an acute myocardial infarction and followed up for a 6-month period A further objective was to determine the incidence of side effects related to long term tocainide therapy

From the University Department of Medical Cardiology Royal Infirmary Glasgow Scotland

Reprint requests Ian Hutton M D University Department of Medical Cardiology Royal Infirmary Glasgow G4 0SF Scotland.

MATERIAL AND METHODS

The patient population was drawn from three hospitals in Glasgow Scotland (Dr D Ballantyne Victoria Infirmary and Dr W S Hillis Stobhill Hospital) The coordinating center was situated in the University Department of Medical Cardiology The Royal Infirmary Glasgow (Dr Ian Hutton) A total of 146 patients under the age of 70 years were entered into the trial There were 121 men and 25 women with an average age of 55 years The two groups were well matched with respect to age site of infarction and estimated size of infarction from enzyme studies as can be seen in Table I The diagnosis of acute myocardial infarction was confirmed clinically and by ECG changes—pathologic Q waves and sequential ST T wave changes and by elevation of the serum enzymes serum glutamic oxaloacetic transaminase (SGOT) lactic dehydrogenase (LDH) and creatine phosphokinase (CPK)

Exclusion criteria were as follows (1) abnormal renal or hepatic function (2) Grade II or III A V block (3) persisting ventricular arrhythmias requiring treatment, (4) continued treatment

0002-8703/80/131017 + 06$00 60/0 © 1980 The C V Mosby Co

Table I Characteristics of tocainide and placebo patients with AMI

	Tocainide (n = 56)	*Placebo (n = 56)*	*Difference*
Sex			
Male	48	41	NS
Female	8	15	
Age (yr)			
Mean	60	61	NS
Range	35-73	30-73	
Previous AMI			
0	48	49	NS
1	6	5	
≥ 2	2	2	
Hypertension	12	15	NS
Diabetes	8	5	NS
Previous heart failure	8	8	NS
Angina > 1 mo	17	17	NS
Previous β blockade	14	10	NS
Delay onset of AMI to drug (hr)			
< 6	18	19	NS
6-24	28	19	
> 24	8	15	
Mean ± SD	13 ± 10.2	16 ± 13.0	NS
Site of AMI			
Anterior	28	25	NS
Inferior	22	22	
Lateral	2	3	
Uncertain	4	6	
S-ASAT max (µkat L)			
< 5.00	38	45	NS
5.00-10.00	15	11	
10.00	3	0	
Mean ± SD	4.11 ± 2.78	2.97 ± 2.17	$P < 0.05$
Median	3.38	2.49	

Ex t information not a ailable for some patients (however < 24 hr

Table II Patients withdrawn from the study because of failure of therapy or potential side effects

Reasons for withdrawal	*Tocainide (n = 56)*	*Placebo (n = 56)*	*Difference*
Death	5	5	NS
VF	3	2	NS
VT	2	2	NS
Asystole > 4 s	1	1	NS
A V block II	2	1	NS
Side effects	9	2	NS
Total	22	13	

Table III Total number of patients with and without frequent VPCs (> 30/hr) and/or VT in the tocainide and placebo groups in any hour during a 24 hour ECG recording during the first 24 hours after 10 days and at 1 and 6 months

Time period	*Arrhythmia present*	*Tocainide* No	*Tocainide* %	*Placebo* No	*Placebo* %	*Difference*
0-24 hr	Yes	6	19	16	47	$P < 0.0$
	No	25	81	18	53	
10 days	Yes	2	9	2	10	NS
	No	20	91	18	90	
1 mo	Yes	4	29	9	47	NS
	No	10	71	10	53	
6 mo	Yes	1	8	8	44	NS
	No	11	92	10	56	

in over 97 of the tapes available in this group These losses and the patient withdrawals account for the varying numbers of patients included in the arrhythmia analysis at different times Contraindications to exercise testing in some patients contributed to a similar variation in the numbers of patients tested

There were no significant differences between the groups in terms of sex distribution age past history previous treatment dela from onset of symptoms t in lu ion and ite of infarct The maximum S AS AT level h w er was significantly higher in the gr up i en tocainide (4.11 ± 2.78 µk t L comp ... 2.97 ± 2.17 $P < 0.05$ Table I

Ten patients gi n toc ai ... io given placebo were withdrawn at varying times during the first days of the study some (nine) according to the protocol and some (11) because of their refusal to participate in the 6 month follow up phase of the study Their withdrawal did not influence the comparability of the two treatment groups Data derived from all patients withdrawn from the study are included in the appropriate analyses up to the time of withdrawal

Deaths The mortality rate of the two groups was similar and the overall mortality in the study was low (8.7%) The mortality remained low (11.7%) when two patients who died after withdrawal from the study (one tocainide patient with aplastic anaemia one placebo patient with VF) were included in the analysis

Except for the patient with aplastic anemia none of the causes of death was unusual or unexpected in view of the primary diagnosis and none was unequivocally due to the administration of tocainide or the study design

experienced by the majority of patients (9 of 12, 75%). However, side effects were transient and overcome gradually by taking the drug with food or by dosage reduction. Side effects precluded long term therapy with tocainide in 2 of the 11 (18%) patients.

Intravenous lidocaine was effective in eight of the nine patients with *myocardial infarction*. Oral tocainide subsequently proved to be effective long term in six (75%) of these lidocaine responders.

No *adverse* conduction abnormalities were detected during this study. However, *none of the* patients underwent *intracardiac* electrophysiology before or during tocainide therapy. Moore et al.[2] have characterized the electrophysiologic activity of tocainide in man.

The effectiveness of tocainide in suppressing VEA/VT in *man* has previously been demonstrated in short term studies by Winkle et al.,[3] Woosley et al.,[4] and Ryan et al.[5] and in long term studies by Winkle et al.[6] and Engler et al.[7] However, in both of these long term studies[6,7] disopyramide was not employed prior to tocainide therapy. Moreover, other antiarrhythmic medications were continued in their patients while on tocainide therapy.

We *recognize* the limitations of 24 hour and *short term* ambulatory ECG *monitoring*,[8] the Lown grading system,[9] the lack of a single accurate and reproducible standard for monitoring arrhythmias, and the lack of intracardiac VT initiation by pacing during tocainide therapy in our patients. However, it appeared that in our highly symptomatic group of patients with VEA/VT resulting from chronic coronary artery disease, both symptomatic episodes of VT and VEA counts and complex forms *decreased* during tocainide therapy.

Tocainide appears to be a promising and useful addition to our limited armamentarium of antiarrhythmic agents. It would appear to be a logical choice for chronic therapy in those patients in whom lidocaine results in VEA/VT suppression. An acceptable level of side effects was noted early in therapy and no long term sequelae resulted from tocainide therapy in our patients.

REFERENCES

1. Lown B, Graboys TB: Management of patients with malignant ventricular arrhythmias. Am J Cardiol 39:910, 1977.
2. Moore EN, Spear JF, Horowitz LN, Feldman HS, Moller RA: Electrophysiologic properties of a new antiarrhythmic drug—tocainide. Am J Cardiol 41:703, 1978.
3. Winkle RA, Meffin PJ, Fitzgerald JW, Harrison DC: Clinical efficacy and pharmacokinetics of a new orally effective antiarrhythmic, tocainide. Circulation 54:884, 1976.
4. Woosley RL, McDevitt DG, Nies AS, Smith RF, Wilkinson GR, Oates JA: Suppression of ventricular ectopic depolarizations by tocainide. Circulation 56:980, 1977.
5. Ryan W, Engler R, LeWinter M, Karliner JS: Efficacy of a new oral agent (tocainide) in the acute treatment of refractory ventricular arrhythmias. Am J Cardiol 43:285, 1979.
6. Winkle RA, Meffin PJ, Harrison DC: Long-term tocainide therapy for ventricular arrhythmias. Circulation 57:1008, 1978.
7. Engler R, Ryan W, LeWinter M, Bluestein H, Karliner JS: Assessment of long-term antiarrhythmic therapy: Studies on the long-term efficacy and toxicity of tocainide. Am J Cardiol 43:612, 1979.
8. Morganroth J, Michelson EL, Horowitz LN, Josephson ME, Pearlman AS, Dunkman WB: Limitations of routine long-term electrocardiographic monitoring to assess ventricular ectopic frequency. Circulation 58:408, 1978.
9. Bigger JT Jr, Wenger TL, Heissenbuttel RH: Limitations of the Lown grading system for the study of human ventricular arrhythmias. Am Heart J 93:727, 1977.

Table IV Frequency and type of VTs induced by exercise at 1, 3, and 6 months after AMI in patients given placebo

Patient No	*1 mo (n = 21)*	*3 mo (n = 19)*	*6 mo (n = 19)*
4	0	0	0
10	–	0	0
16	0	Monofocal paired ~40/min (bigeminy)	Monofocal paired ~30/min (bigeminy)
26	Multifocal paired ~10/min	Multifocal ~30/min	Monofocal paired ~30/min (bigeminy)
30	Monofocal < 5/min	–	–
36	Monofocal paired ~50/min	VT repeated short bursts ~3 sec each	Monofocal ~15/min
43	0	0	0
46	0	0	0
55	Monofocal, paired ~60/min (bigeminy)	Monofocal paired ~40/min	Monofocal, ~2[illegible]/min (bigeminy)
56	0	0	Monofocal < 5/min
62	0	Monofocal ~15/min	Monofocal ~20/min
64	Monofocal < 5/min	0	VT two bursts 25 sec each
69	0	0	Monofocal ~25/min
73	0	Monofocal < 5/min	0
80	0	0	0
86	0	0	0
91	Monofocal paired ~10/min	–	–
95	0	0	Monofocal < 5/min
100	0	0	0
101	0	0	0
105	Monofocal paired ~10/min	0	0

Withdrawals Twenty two patients given tocainide and 13 given placebo were withdrawn from the study because of failure of therapy or potential side effects The difference between the groups was primarily attributable to the greater number of patients withdrawn from tocainide because of side effects (nine compared to two) The number of patients withdrawn because of VT asystole or A V block was essentially the same in both groups (Table II)

Five patients in the tocainide group developed *significant* VT One patient developed rapid VT 4 minutes after the start of the tocainide infusion and consequently had only a very low plasma level when withdrawn Therefore the failure of tocainide therapy in this patient is questionable However the bursts of VT that were noted before the injection deteriorated into sustained rapid VT after tocainide Although this is often the natural history of this arrhythmia it is possible that the low concentration of tocainide produced a more rapid reentry circuit than was possible in the absence of the drug Although the patient did not respond to procainamide he did respond to disopyramide

Two patients developed VF 4 5 hours and 11 days respectively after inclusion in the study Plasma tocainide concentrations were low in both cases Lidocaine was ineffective in both patients and the arrhythmias responded to procainamide One patient developed VF despite having a plasma tocainide concentration in the middle of the suggested therapeutic range This patient s arrhythmia was also refractory to lidocaine but responded to procainamide One patient developed sustained VT at a rate of 180/min despite a therapeutic plasma tocainide concentration The arrhythmia was also refractory to quinidine and procainamide Since it was possible to terminate the arrhythmia repeatedly with intravenous lidocaine the patient was again given tocainide but an increased dosage This successfully controlled the arrhythmia

Spontaneous VTs observed on continuous ECG recordings Over the first 24 hours continuous ECG recordings were obtained from 31 tocainide and 34 placebo treated patients The total number of recorded hours was 1 291 The tocainide treated patients had significantly fewer recorded hours containing VPCs than did the

III Chronic tocainide therapy studies

A prospective randomized trial of tocainide in patients following myocardial infarction

B C Bastian M B, Ch B P W Macfarlane B Sc Ph D J H McLauchlan M B Ch B D Ballantyne M D R Clark M B Ch.B W S Hillis M B Ch B A P Rae B Sc M B and I Hutton M D Glasgow Scotland

One hundred forty six patients with recent acute myocardial infarction were grouped at random into those treated with tocainide an oral analogue of lignoca ne or placebo and followed up for 6 months In addition to standard investigations a 24-hour ambulatory taped ECG recording was obtained prior to randomization and thereafter at 2 8 16 and 24 hours after discharge The ECGs were analyzed by means of an automated computerized reporting system Forty two patients had significant ventricular arrhythmias 10 of whom had effect ve plasma levels of toca nide compared with 27 patients on placebo ($P < 0\ 005$) In the placebo patients with increasing mobilization there was a consistent rise in the number of ventricular ectopic beats per day There was no such increase in the tocainide patients ($P < 0\ 01$) S de effects were few and the incidence of central nervous system s de effects was s milar in both the tocainide and placebo groups There was no conclusive evidence of myocardial depression heart rate and blood pressure being unchanged over the 6 month period Although ventricular arrhythmias were suppressed the number of patients in the study was too small to draw conclus ons regard ng the mortality rate

The risk of sudden death is increased in patients with coronary heart disease particularly in patients with ventricular ectopic beats It therefore seems reasonable to try and prevent such ventricular arrhythmias Tocainide is an analogue of lignocaine and has been shown to be an effective antiarrhythmic agent in animals and in several preliminary studies in patients[6-9] It is almost 100% absorbed after oral administration and has a plasma half life of approximately 12 hours in patients with normal renal and hepatic function[11,12] The purpose of the present study was to evaluate the effects of tocainide on the prevention of ventricular arrhythmias in a placebo controlled trial in patients recovering from an acute myocardial infarction and followed up for a 6-month period A further objective was to determine the incidence of side effects related to long term tocainide therapy

From the University Department of Medical Cardiology Royal Infirmary Glasgow Scotland

Reprint requests Ian Hutton M D University Department of Medical Cardiology Royal Infirmary Glasgow G4 0SF Scotland.

MATERIAL AND METHODS

The patient population was drawn from three hospitals in Glasgow Scotland (Dr D Ballantyne Victoria Infirmary and Dr W S Hillis Stobhill Hospital) The coordinating center was situated in the University Department of Medical Cardiology The Royal Infirmary Glasgow (Dr Ian Hutton) A total of 146 patients under the age of 70 years were entered into the trial There were 121 men and 25 women with an average age of 55 years The two groups were well matched with respect to age site of infarction and estimated size of infarction from enzyme studies as can be seen in Table I The diagnosis of acute myocardial infarction was confirmed clinically and by ECG changes--pathologic Q waves and sequential ST T wave changes and by elevation of the serum enzymes serum glutamic oxaloacetic transaminase (SGOT) lactic dehydrogenase (LDH) and creatine phosphokinase (CPK)

Exclusion criteria were as follows (1) abnormal renal or hepatic function (2) Grade II or III A V block (3) persisting ventricular arrhythmias requiring treatment (4) continued treatment

Table V Frequency and type of VTs induced by exercise at 1 3 and 6 months after AMI in patients given tocainide

Patient No	*1 mo (n = 15)*	*3 mo (n = 15)*	*6 mo (n = 14)*
1		—	0
5	0	0	0
15	0	Monofocal < 5/min	Monofocal < 5/min
	Multifocal paired ~ 10/min		
25	0	0	0
[illegible]	0	0	0
37	0	0	—
[illegible]	0	0	0
44	0	0	0
[illegible]	—	0	0
[illegible]	0	0	0
[illegible]	0	0	0
[illegible]	0	0	—
[illegible]	0	0	0
[illegible]	0	0	0
[illegible]	Monofocal ~20/min (bigeminy)	0	0
[illegible]	0	0	0

placebo treated patients Frequent VPCs and/or VTs on any occasion during the first 24 hours occurred in 19% of tocainide treated patients and in [illegible] of those given placebo This difference is statistically significant ($P < 0.05$) The percentage of patients with VT was significantly greater in the placebo group (41% compared to 13% $P < 0.05$)

One and six months after inclusion in the study fewer patients in the tocainide group had VTs but because of the small number of observations this difference did not reach statistical significance (Table III) Notwithstanding this the number of hours during which arrhythmias occurred was significantly less in the tocainide group at all assessment times except at 10 days

Exercise induced ventricular arrhythmias There were no significant differences between the maximum workloads achieved by the two groups at any observation period nor between the heart rates and systolic blood pressures In general the reasons for discontinuation of exercise were similar in the two groups The development of VTs however resulted in discontinuation of the exercise test in three patients given placebo on four occasions while in the tocainide [illegible] exercise tests were discontinued be[illegible] development of such arrhythmias

More patients in the placebo group developed VTs on exercise (Tables IV and V) Although the difference between the groups did not reach statistical significance at 1 and 3 months after AMI the incidence of arrhythmic events in the placebo group was significantly greater at the 6 month exercise test ($P < 0.05$) A significantly greater number of patients in the placebo group had exercise arrhythmias on one or more occasions (13 compared to two $P < 0.01$) Since VT did not occur after exercise in tocainide treated patients, the data suggest that tocainide was associated with a reduced incidence of serious ventricular arrhythmias in these patients The greater number of patients with frequent paired and/or multifocal VPCs induced by exercise in the placebo group also supports this conclusion

Tolerability No clinically important changes in mean blood pressure or heart rate occurred within the 60 minute period following the injection of tocainide There were no significant differences in mean blood pressure and heart rate between the tocainide and placebo treated groups 10 days 1 month 3 months and 6 months after the start of treatment Side effects following intravenous injection were more common in the tocainide treated patients (n = 17) than in those receiving placebo (n = 3)

CNS symptoms were the most common side effects seen in the tocainide group and usually consisted of paresthesias described as a numbness in the throat tingling sensations in the lips a feeling of cold or warmth and in a few cases a tingling sensation in the arms CNS side effects were all reported as mild or moderate except in one patient who developed confusion 5 minutes after the start of tocainide injection (250 mg) The infusion was stopped and the patient was withdrawn from the study The symptoms disappeared completely 10 to 15 minutes after the injection was terminated

Gastrointestinal complaints were the next most common side effects in patients given tocainide These usually included mild to moderate nausea followed by vomiting

Cardiovascular side effects occurred in four patients in association with intravenous tocainide administration and consisted of a fall in blood pressure and heart rate The injection was completed when the blood pressure stabilized following atropine and/or a short break in the infusion

Withdrawals due to side effects Nine patients

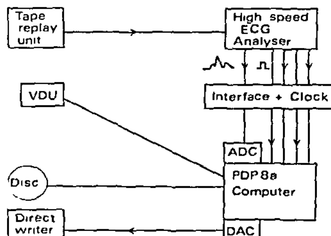


Fig 1 The tape replay computer analysis system ADC = analogue digital convertor DAC = digital analogue convertor VDU = visual display unit

with β adrenergic receptor blocking drugs and (5) persisting angina pectoris

Patients were considered for entry into the study 7 to 10 days after hospital admission for acute myocardial infarction The use of cardiac glycosides and diuretics was not considered a contraindication A detailed history was obtained and physical examination performed A 12 lead ECG and chest x ray film were taken Blood was taken for standard hematologic and biochemical screening for hepatic and renal abnormalities and an antinuclear antibody (ANA) titer A 24 hour taped ECG was recorded at a time when the patient was ambulatory prior to hospital discharge Written consent was obtained from the patient and either tocainide 200 mg t i d or placebo was given in a randomized double blind fashion The patients were reviewed as outpatients at 2 8 16 and 24 weeks after discharge and again at 25 weeks when medication had been discontinued

The preceding investigations including ANA and 24 hour ECG recording were repeated at each outpatient visit In addition information regarding possible adverse events was carefully collected at each clinic visit Blood was taken for plasma tocainide levels approximately 2 to 3 hours after administration of the medication

Patients were withdrawn from the study if treatment failed i e if significant ventricular arrhythmias developed ' and if an adverse event occurred such as left heart failure angina pectoris requiring the use of β adrenergic receptor blocking drugs or side effects of such severity as to be unacceptable to the patient developed

Table I Clinical details of patient population

Clinical data	Tocainide (n = 72)	Placebo (n = 71)
Sex	60 males 12 females	61 males 13 females
Age (yr)	55 6 ± 1	55 1 ± 1
Site of myocardial infarction	Inferior 37 Anterior 35	Inferior 40 Anterior 34
Peak cardiac enzyme CPK (U/L)	1 360 ± 200	1 133 ± 266

Twenty four-hour ECG analysis ECGs were taped by means of Oxford Medical Instruments Medilog 24 hour recorders The Oxford tape unit was linked to a high speed ECG analyzer (Pathfinder) of Reynolds Medical Electronics A technician teaches the analyzer the morphology of the normal QRS complex and analysis thereafter is automatic once the appropriate triggering levels have been set The outputs from the high speed analyzer are interfaced to a PDP8A minicomputer (Fig 1) The particular outputs utilized are the logic pulse which indicates whether a QRS complex is normal or abnormal In addition the ECG signal itself is fed from the replay unit to the computer

The interface has been designed to lengthen the logic pulse which indicated the morphology of the QRS complex It also filters the ECG signal to remove high frequency noise In addition it contains a clock used to control analogue to digital conversion of the ECG signal at a rate equivalent to 125 samples/sec real time Arrhythmic events can be detected and automatically printed by the Pathfinder and/or by the computer The printout from the computer provides a breakdown of the 24 hour recording into 15 minute periods for which the average heart rate and frequency of ventricular ectopic beats supraventricular tachycardia and ventricular tachycardia are produced Thus the system automatically captures arrhythmic events produces an interpretation and outputs the relevant ECG strip[13]

The accuracy of the reporting system is dependent on the Reynolds Pathfinder and this has been reported in a number of studies[14] The sensitivity of the method will depend on the population studied and for the identification of the aberrant beats the sensitivity is in the order

total were withdrawn from the tocainide study because of side effects One patient suffered nausea and vomiting two developed rashes five had different types of CNS side effects and one developed aplastic anemia The gastrointestinal and in three cases the CNS side effects were finally considered to be caused by tocainide as were the rashes

In one patient aplastic anemia was diagnosed 36 days after the start of treatment with tocainide This patient had serious AMI resulting in congestive cardiac failure which was treated with furosemide spironolactone digoxin and prazosin The patient was readmitted with septicemia secondary to agranulocytosis Tocainide and prazosin were withdrawn and the patient died of VF following the development of cardiogenic shock within 24 hours of admission The etiology of the aplastic anemia is not known but tocainide furosemide spironolactone and prazosin could be implicated as a cause of the aplastic anemia and agranulocytosis although it is not possible to determine whether any of these agents singly or in combination were cause and effect related

Plasma tocainide concentrations The mean and individual plasma tocainide concentrations obtained in a random sample of patients from both treatment centers showed that the dosage regime produced mean plasma concentrations within the suggested therapeutic range (18 to 45 μmol/L) at all sampling times

During the 6 month follow up period the vast majority of patients had tocainide concentrations within this range suggesting that compliance was good in general

Discussion

Tocainide is a primary amine which in many respects is closely related to lidocaine

However in contrast to lidocaine tocainide is rapidly and completely absorbed from the gastrointestinal tract and the first pass effect is negligible In animal studies tocainide has been found to be effective by both the intravenous and oral route for suppressing experimentally induced cardiac arrhythmias[1,2] Several studies of the efficacy of the drug in ventricular arrhythmias of varying origin have been carried out in humans Winkle et al[3] found that serious chronic ventricular arrhythmias refractory to other antiarrhythmic agents could be controlled with tocainide in appropriate doses The study also showed that there was a correlation between the concentration of the drug in plasma and the antiarrhythmic effect Other investigators have reported similar results These studies have mainly comprised patients with arrhythmias due to coronary heart disease and previous AMI Experience with the use of tocainide for suppression of arrhythmias in the acute phase of myocardial infarction is still limited Since the drug has been shown to have attractive electrophysiologic and hemodynamic[6] qualities it should possibly be advantageous to use it in patients with AMI thereby combining the lidocaine like characteristics with oral availability In a study of the pharmacokinetic effects of tocainide on patients with AMI it was shown that it was possible to achieve the results of Winkle et al who suggested obtaining rapid therapeutic plasma concentrations by combining intravenous and oral administration This plasma level was maintained during steady state conditions and the regimen did not induce any important untoward effects It was therefore considered appropriate to perform a controlled investigation of the effects of tocainide in AMI

In the present study tocainide did not prevent VF symptomatic VT or sudden death in patients with AMI Because of the small number of patients enrolled in the study and the surprisingly low overall mortality rate it is not possible to conclude on statistical grounds that tocainide lacks the ability to prevent these events Some of the patients who developed serious ventricular arrhythmias had low plasma tocainide concentrations at the time of the event and in one patient VT which occurred despite an apparently adequate plasma tocainide concentration was controlled by increasing the dosage This suggests that it may be possible to improve arrhythmia control by increasing the dosage within the limits of patient tolerance This is obviously not possible in a double blind study The majority of patients achieved plasma tocainide concentrations in the range of 18 to 45 μmol/L as was expected from our initial pharmacokinetic study of patients with AMI[9]

The present study may indicate that the suggested therapeutic range is not generally valid but that higher concentrations are desirable in some patients Individual titration of the tocainide dose until the highest level tolerated has been found might be preferrable Further studies involving a greater number of patients and individually chosen dosages are thus necessary to determine whether or not tocainide can prevent VF symp

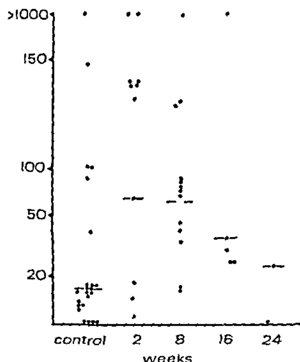


Fig 2 Number of ventricular ectopic beats found in 24 hours in placebo treated patients expressed on a log scale The bars indicate the median value

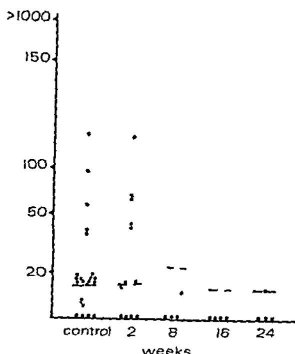


Fig 3 Number of ventricular ectopic beats found in 24 hours in tocainide treated patients expressed on a log scale The bars indicate the median value

of 97% The specificity however may appear to be exceptionally high if the number of false positive aberrant beats is related to the total number of beats in the 24 hour period With the adoption of this form of analysis specificity may be regarded as high as 99 9% The arrh th as detected by the computer were ind r r analyzed and confirmed visually by t observers

Plasma tocainide levels were estimated Astra Clinical Research Center Edinburgh effective p na level of tocainide would ap to be > 3 ml

Statistic lysis The basic design was of a group comp between two treatments Statistical test analysis were a χ test and Student s p A P value of < 0.05 was considered t ant

Results

Forty two tients had significant ventricular nd were withdrawn from the study patients had effective plasma le ompared with 27 patients receiv nide thus significantly reduced the incidence of serious ventricular arrhythmias ($P < 0.005$)

There was considerable individual variation in the number of ventricular ectopic beats in any 24 hours The range was 0 to 6 547 ectopic beats in 24 hours Consequently the results were expressed as the median number of ventricular ectopic beats per patient per day In the placebo patients the median value on admission was 14 ventricular ectopic beats per patient per day and increased to 67 a 68 at 2 and 4 weeks respectively This increase was maintained throughout the period of the study (Fig 2) In the tocainide patients there was no increase in the number of ventricular ectopic beats per patient The median number of ventricular ectopic beats per patient on admission was 11 and there was little or no increase—12 22 9 and 9 (Fig 3) Thus tocainide produced a significant reduction in the number of ventricular ectopic beats found with increasing mobilization in these postmyocardial infarction patients treated with placebo ($P < 0.01$) The hemodynamic effects of tocainide can be seen in Fig 4 There was little or no change in systemic blood pressure or in heart rate throughout the 6

Table V. Frequency and type of VTs induced by exercise at 1, 3, and 6 months after AMI in patients given tocainide

Patient No.	1 mo (n = 15)	3 mo (n = 15)	6 mo (n = 14)
1		—	0
5	0	0	0
15	0	Monofocal < 5/min	Monofocal < 5/min
	Multifocal, paired, ~10/min		
25	0	0	0
27	0	0	0
37	0	0	—
[illegible]	0	0	0
44	0	0	0
53	—	0	0
57	0	0	0
58	0	0	0
6[illegible]	0	0	—
70	0	0	0
74	0	0	0
[illegible]	Monofocal ~20/min (bigeminy)	0	0
[illegible]	0	0	0

placebo-treated patients. Frequent VPCs and/or VTs on any occasion during the first 24 hours occurred in 19% of tocainide treated patients and in 47% of those given placebo. This difference is statistically significant ($P < 0.05$). The percentage of patients with VT was significantly greater in the placebo group (41% compared to 13%, $P < 0.05$).

One and six months after inclusion in the study, fewer patients in the tocainide group had VTs, but because of the small number of observations this difference did not reach statistical significance (Table III). Notwithstanding this, the number of hours during which arrhythmias occurred was significantly less in the tocainide group at all assessment times except at 10 days.

Exercise induced ventricular arrhythmias. There were no significant differences between the maximum work loads achieved by the two groups at any observation period, nor between the heart rates and systolic blood pressures. In general, the reasons for discontinuation of exercise were similar in the two groups. The development of VTs, however, resulted in discontinuation of the exercise test in three patients given placebo on four occasions, while in the tocainide group no exercise tests were discontinued because of the development of such arrhythmias.

More patients in the placebo group developed VTs on exercise (Tables IV and V). Although the difference between the groups did not reach statistical significance at 1 and 3 months after AMI, the incidence of arrhythmic events in the placebo group was significantly greater at the 6-month exercise test ($P < 0.05$). A significantly greater number of patients in the placebo group had exercise arrhythmias on one or more occasions (13 compared to two, $P < 0.01$). Since VT did not occur after exercise in tocainide treated patients, the data suggest that tocainide was associated with a reduced incidence of serious ventricular arrhythmias in these patients. The greater number of patients with frequent paired and/or multifocal VPCs induced by exercise in the placebo group also supports this conclusion.

Tolerability. No clinically important changes in mean blood pressure or heart rate occurred within the 60 minute period following the injection of tocainide. There were no significant differences in mean blood pressure and heart rate between the tocainide and placebo treated groups 10 days, 1 month, 3 months, and 6 months after the start of treatment. Side effects following intravenous injection were more common in the tocainide-treated patients (n = 17) than in those receiving placebo (n = 3).

CNS symptoms were the most common side effects seen in the tocainide group and usually consisted of paresthesias described as a numbness in the throat, tingling sensations in the lips, a feeling of cold or warmth, and in a few cases a tingling sensation in the arms. CNS side effects were all reported as mild or moderate except in one patient who developed confusion 5 minutes after the start of tocainide injection (250 mg). The infusion was stopped and the patient was withdrawn from the study. The symptoms disappeared completely 10 to 15 minutes after the injection was terminated.

Gastrointestinal complaints were the next most common side effects in patients given tocainide. These usually included mild to moderate nausea followed by vomiting.

Cardiovascular side effects occurred in four patients in association with intravenous tocainide administration and consisted of a fall in blood pressure and heart rate. The injection was completed when the blood pressure stabilized following atropine and/or a short break in the infusion.

Withdrawals due to side effects. Nine patients

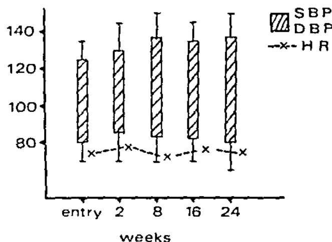


Fig 4 Effects of tocainide on systolic and diastolic blood pressure and heart rate The results are expressed as the mean and the standard error of the mean

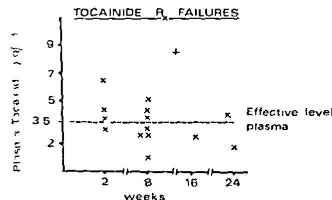


Fig 5 Plasma tocainide levels in patients who developed significant ventricular arrhythmias Dotted line indicates that the effective plasma level of tocainide is greater than 3 5 µg/ml + indicates sudden death in a patient

months Although this evidence is far from conclusive tocainide would not appear to produce a significant depressant effect on the myocardium

There was a high incidence of new cardiovascular events (15%) with four patients sustaining a further myocardial infarction and 18 patients developing angina pectoris of such severity as to justify the use of β adrenergic receptor blocking drugs

Fifteen patients were withdrawn from the trial because of unacceptable side effects that were considered by the attending physician to be related to their medication The detailed results are found in Tables II and III It can be seen that the incidence of lightheadedness in dyspepsia appeared to be higher in the tocainide treated patients A severe skin rash appeared in 3 of the 71 patients treated with tocainide There was a surprising similar incidence of central nervous system (CNS) symptoms in both treatment groups These complaints consisted of paresthesia and twitching with no objective clinical evidence of CNS pathology One patient developed allergic alveolitis while being treated with tocainide the drug was discontinued with some improvement but only after corticosteroid therapy was his lung function restored to near normal with improvement in symptoms

Neither significant ANA titers nor abnormal renal or hepatic function was found in any of the tocainide treated patients

Patient compliance as assessed by tocainide blood levels was excellent In three of the patients withdrawn from the study because of unacceptable side effects, with no objective evidence of pathology there was little or no tocainide found in the plasma

It is of interest that 7 of the 15 patients did not have effective plasma tocainide levels and significant ventricular arrhythmias were found in these patients It is perhaps of greater interest that significant ventricular arrhythmias could still occur despite high plasma levels of tocainide (Fig 5) Indeed sudden death occurred in a patient who had a plasma level of 9 1 µg/ml

Discussion

This study has demonstrated that tocainide is an effective antiarrhythmic agent in patients followed up for 6 months after an acute myocardial infarction The incidence of significant ventricular arrhythmias was reduced as was the increase in ventricular ectopic beats found in such patients known to have peptic ulceration or gastroesophageal reflux There was no conclusive evidence of a depressant effect on the myocardium

Adverse reactions contraindications lack of effectiveness and frequent drug administration with established oral antiarrhythmic therapy have stimulated the search for additional orally effective antiarrhythmic drugs In Europe amiodarone is used extensively and suppresses both supraventricular and ventricular arrhythmias It is particularly effective in the treatment of tachyarrhythmias associated with the Wolff Parkinson White syndrome The major side effect of

the transducer resolution still remains to be solved

More recently Silverman and associates[1] reported on the four chamber view in congenital heart diseases using an electronic sector scan In addition Ports and associates[11] measured the displacement of the STL in Ebstein s anomaly with this method It appears to be practical to utilize the apical cross section for the four chamber view according to their method when assessing the displacement of the STL from the right atrioventricular ring

However this approach also has its limitations In our experience we could not measure the displacement of the STL in the four chamber view in three out of the 11 patients in spite of the specific angiographic findings In one of the three the STL was not identified from the four chamber view whereas the rudimentary STL was found in the three chamber view by angulating the transducer in the direction B from the cardiac apex (patient M T) In another of the three patients (T T) the four chamber view disclosed no displacement of the STL although it was measured as 1 5 cm at cardiac operation

The downward displacement of the STL in our study was less than that reported by Ports and associates[11] This is probably attributable to the fact that there were milder forms of the anomaly in the majority of the patients examined Moreover attention should be paid to the differentiation of the STL from the trabeculae in the right ventricle The rudimentary STL should not be confused with other intracardiac structures To separate the STL from other echo origins it is important to carefully observe the movement of each component of subvalvular structures using the cinematography or video system Finally the downward displacement of the STL should be assessed in comparison with the findings at operation or autopsy in order to obtain the most appropriate cross section for the measurement

With regard to the subxiphoid approach Chang and Feigenbaum[1] reported they could overcome the limitations of the standard technics of M mode echocardiography It is well known that the patient with emphysema or a large barrel chest is very difficult to examine with the transducer along the left sternal border

Matsukubo and associates applied this method to the measurement of the right ventricular wall thickness Furthermore it has been extended to the field of cross sectional echocardiography using electronic sector scanning[13]

In Ebstein s anomaly the right sided heart chambers are extremely enlarged making it difficult to visualize the over all right ventricle from the apex to the base In this connection the subxiphoid approach seems useful to observe the right ventricular apex to the base as well as the tricuspid subvalvular apparatus However little has been reported on this and this is the reason we chose to undertake the present study

In order to clearly describe the tricuspid subvalvular structures we adjusted the gain setting and deepened the focal point in comparison with standard cross sectional technics The interpretable images were available with the subxiphoid approach except for the patients with liver enlargement or tight abdominal wall In contrast the displacement of the STL was detected by this technic only in three instances Thus the four chamber view is thought superior to the subxiphoid approach in the detection of the distorted STL whereas the subxiphoid cross section is recommended when other approaches are not suitable to obtain intracardiac information

Summary

Apex and subxiphoid cross sectional echocardiography was performed with an electronic sector scan on 11 patients having Ebstein s anomaly isolated or associated with other cardiac diseases For control study 10 normal subjects and 10 ASD patients were similarly examined

In the apical four chamber view the displacement of the STL was measured in end diastole using 8 mm cinematography It ranged from 1 4 to 3.2 cm with an average of 2 1 ± 0 5 cm in eight out of the 11 patients whereas in control subjects there was no displacement of the STL

From the apical three chamber view of the right side of the heart the downward displacement of the STL into the right ventricular cavity was also clearly visualized as well as the tricuspid valve ring Thus the right sided heart was seen to be divided into the functional and atrialized right ventricles and the right atrium by the displacement of the STL

In addition the CT inserting into the ATL was observed in five cases from the three chamber view and in four instances from the four chamber view

The interpretable subxiphoid cross sectional

images were obtained in nine of the 11 patients The right and left sides of the heart were widely visualized and the elongated ATL was fully observed from the tip to the thickened root Moreover the CT inserting into the ATL was visualized in six out of the nine patients

We are grateful to Mr Yoshihisa Kitamura for his technical assistance and to Mr John M Shields for correcting the English in this paper

REFERENCES

1 Lundstrom N R. Echocardiography in the diagnosis of Ebstein s anomaly of the tricu pid valve Circulation 47 597 1973
2. Lev M., Liverthson R R., Joseph R H., Seten C E., Kunske R. D., Eckner F A., and Miller R A The pathologic anatomy of Ebstein s disease Arch Pathol. 90 334 1970
3 Anderson K. R., and Lie J T Pathologic anatomy of Ebstein s anatomy of the heart revisited Am J Cardiol 41 739 19"8
4 Genton E., and Blount S G The spectrum of Ebstein s anomaly Am Heart J 73 39; 1967
5 Takavasu S., Obunai, Y., and Konno S Clinical classi fication of Ebstein s anomaly Am Heart J 95 154 1978
6 Farooki, Z. Q., Henry J G., and Green, E W Echocar diographic spectrum of Ebstein s anomaly of the tricus pid valve Circulation 53 63 1976
7 Yuste P Minguez, I., Aza, V., Senor J., Asin E., and Martinez Bordiu, C Echocardiography in the diagnosis of Ebstein s anomaly Chest 66 273 1974
8 Kotler M N Tricuspid valve in Ebstein s anomaly Circulation 49 194 1974
9 Tajik A. J., Gau G T., Giuliani, E R., Ritter D G and Schattenberg T T Echocardiogram in Ebstein s anomaly with Wolff Parkinson White pre-excitation syndrome type B Circulation 47 813 1973
10 Silverman N H., and Schiller N B Apex echocardiography A two-dimensional technique for evaluating congenital heart disease Circulation 57 503 1978
11 Ports, T A., Silverman N H., and Schiller N B. Two-dimensional echocardiographic asses ment of Ebstein s anomaly Circulation 58 3,6 19"8
12. Machii K., Toda E., Ida Y., and Iinuma, K. Cross-sectional echocardiography by real time phased array sector scanning system Special reference to the newly devised recording technique from the apex of the heart Jap J Med. Ultrasonics 5 31 19"8 (in Japanese)
13 Chang S and Feigenbaum H Subxiphoid echocardiography J Clin Ultrasound 1 14 1973
14 Matsukubo H., Matsuura T., Endo N., Asayama, J Watanabe T., Furukawa K., Kunishige H Katsume, H., and Ijichi, H Echocardiographic measurement of right ventricular wall thickness. A new application of subxiphoid echocardiography Circulation 56 2,8 19"
15 Nanda, N C., and Gramiak, R. Two-dimensional echocardiography in Clinical echocardiography St. Louis, 1978 The C V Mosby Company p 369
16 Matsumoto M. Mat uo H Nagata, S Hamanaka Y Fujita T., Kawashima Y., Nimura Y and Abe H. Visualization of Ebstein s anomaly of the tricuspid valve by two-dimensional and standard echocardiography Circulation 53 69 19"6
17 Hirschklau M J., Sahn D J., Hagan A. D Williams, D E., and Friedman W F Cross-sectional echocardiographic features of Ebstein s anomaly of the tricuspid valve Am J Cardiol. 40 400 1977

Table II Side effects of therapy

Side effects	Lightheadedness	Rash	Gastro-intestinal	Affect	CNS
Tocainide	7	3	10	4	5
Placebo	2	0	6	2	5
Withdrawal					
Tocainide	2	2	2	0	2
Placebo	1	0	0	0	0

this compound is the finding of corneal deposits in nearly all of the patients These deposits usually do not interfere with vision but may upset corneal metabolism [1]

Disopyramide is similar in its action to both quinidine and procainamide and like amiodarone is useful in the management of both supraventricular and ventricular arrhythmias Anticholinergic side effects including dry mouth blurred vision and urinary retention are not infrequent [1] Significant myocardial depression in patients with left ventricular dysfunction has recently been reported by Podrid et al

Mexiletine has similar electrophysiologic properties to lignocaine and thus is useful in the management of ventricular arrhythmias [1] Chamberlain has recently reported that mexiletine effectively suppressed ventricular arrhythmias in a group of postmyocardial infarction patients without however influencing the mortality rate A number of side effects have been reported consisting either of gastrointestinal problems such as nausea and vomiting or CNS problems with tremor ataxia and parasthesia

Tocainide would appear to be effective and to have relatively few side effects in a dosage of 400 mg t i d It is of interest that there were a considerable number of nonspecific side effects related to placebo therapy in this postmyocardial infarction group of patients CNS side effects might be anticipated with this analogue of lignocaine but in the dosage used in this study there was no objective evidence of CNS pathology despite complaints of lightheadedness tremor and paresthesia in some patients The similar incidence of CNS symptoms in the placebo group of patients emphasizes the need for caution in relating side effects to any form of drug therapy

It was noted that significant ventricular arrhythmias could occur despite adequate circulating levels of tocainide The particular assay used for the estimation of plasma levels was different from that used by other workers and the effective plasma level of tocainide in this study would appear to be a level greater than 3 5 μg/ml Winkle et al [8] have previously reported that tocainide was successful in controlling ventricular arrhythmias in 53% of patients proving unresponsive to quinidine procainamide or propranolol As in this study significant ventricular arrhythmias and sudden death could still occur despite more than adequate circulating blood levels of tocainide

Table III Side effects of therapy

Side effects	Malaise	Allergic lung disease	Insomnia	Polymyalgia
Tocainide	0	1	2	0
Placebo	2	0	?	1
Withdrawal				
Tocainide	0	1	1	0
Placebo	1	0	0	1

These results suggest that tocainide is a safe and effective antiarrhythmic agent in postmyocardial infarction patients but a larger number of patients is required before we can conclude that a reduction in ventricular arrhythmias is associated with a reduced mortality rate

REFERENCES

1 Hinkle LE Jr Carver ST Stevens M The frequency of asymptomatic disturbances or cardiac rhythm and conduction in middle-aged men. Am J Cardiol 24 629-50 1969
2 Chiang BN Perlman LV Fulton M Ostrander LD Epstein F H Predisposing factors in sudden death in Tecumseh, Michigan. Circulation 46.31 7 1970
3 Report of the Coronary Drug Project Research Group The prognostic importance of the ECG following myocardial infarction Ann Intern Med 77 677-89 1972
4 Kotler MN Tabatznik B Mower MM Tominaga S Prognostic significance of ventricular ectopic beats with respect to sudden death in the late post infarction period. Circulation 47 959 66 1973

Tocainide for drug resistant ventricular arrhythmias Efficacy, side effects, and lidocaine responsiveness for predicting tocainide success

Roger A Winkle M D Jay W Mason M D and
Donald C Harrison M D *Stanford Calif*

Tocainide therapy has been evaluated in 38 patients with ventricular arrhythmias Thirty-one had recurrent sustained ventricular tachycard a and/or fibr llation and 29 required prior cardioversions These arrhythm as could not be managed with quinidine procainamide disopyramide or propranolol Tocainide doses averaged 1 500 *mg/day (range 600 to 2 400) and the majority of pat ents had plasma* concentrations from 6 to 12 μg/ml Twenty two patients (61 /) had their arrhythmias controlled with tocainide and 16 (39 /) did not Tocainide dose and plasma concentrat ons were s milar for responders and nonresponders Lidocaine was effective in 26 patients and 16 (63 /) of these had their arrhythmias controlled with tocainide Of 12 patients in whom lidocaine was known to be ineffect ve or who had not been previously treated only two (17 /) had arrhythmias controlled with toca n de ($P < 0\ 02$) S de effects occurred in approximately two thirds of patients but required discontinuation of long term tocainide in only three patients

Tocainide is a lidocaine analogue that is effective for treating ventricular arrhythmias It has nearly complete bioavailability and a plasma half life averaging 13 5 hours Plasma concen tration is directly proportional to dose in individ ual patients and there is a narrow range of intersubject variation of plasma concentration for any dose Electrophysiologically tocainide resembles lidocaine and its primary hemody namic effect after intravenous dosing is a modest elevation of vascular resistance resulting in a slight rise in arterial pressure

This study reports our experience with the use of long term tocainide in a group of patients with severe ventricular arrhythmias that could not be managed with other generally available antiar rhythmic drugs We will examine the efficacy and side effects and the value of lidocaine responsive ness for predicting arrhythmia control with tocainide

F om th Card ology D vision, Stanf rd Uni ers ty School of Medicin Sta ford Cal f

Reprint requests Roge A Winkle M D Cardiology Di is n St n f rd Un ersity School f Med ne Stanf rd CA 94305

Methods

Thirty eight patients with ventricular arrhyth mias are the subjects of this report This report includes and provides further follow up on the 17 patients reported on in 1978 Each patient had ventricular arrhythmias that could not be man aged adequately with currently available antiar rhythmic drugs All gave written informed con sent and the therapy was approved by the Stan ford Human Subjects Committee

For patients with frequent recurrent episodes of sustained ventricular tachycardia or ventricu lar fibrillation tocainide therapy was considered successful when control of these severe occur rences was established For patients with ventric ular ectopic activity tocainide was considered successful when there was nearly complete elimi nation of ventricular ectopic beats

Initial dosing with tocainide was undertaken for most patients at 400 mg every 8 hours The

0002-8 03/80/131031 + 06$00 60/0 © 1980 The C V Mosby Co

5 Duce BR Smith ER Boyes RN Byrnes EW The acute antiarrhythmic and toxic effects of W 3609 in mice and dogs Pharmacologist 15 192 1973
6 Coltart DJ Berndt TB Kernoff R Harrison DC Antiarrhythmic and circulatory effects of Astra W 3609 Am J Cardiol 34 35-41 1974
7 Moore EN Spear JP Horowitz LW Feldman HS Moller RH Electrophysiological properties of a new antiarrhythmic drug—tocainide Am J Cardiol 41 703-09 1978
8 Winkle RA Meffin PJ Fitzgerald JW Harrison DC Clinical efficacy and pharmocokinetics of a new orally effective antiarrhythmic tocainide Circulation 54 884 89 1976
9 Winkle RA Meffin PJ Harrison DC Long term tocainide therapy for ventricular arrhythmias Circulation 57 1008 16 1978
10 Ryan W Engler R Lewinter M Karliner JS Efficacy of a new oral agent (tocainide) in the acute treatment of refractory ventricular arrhythmias Am J Cardiol 43 285 91 1979
11 Lalka D Meyer MB Duce RR Elvin AT Kinetics of the oral antiarrhythmic lidocaine congener Tocainide Clin Pharmaco Ther 19 757 66 1976
12 Boyes R N Meyer M B Tweddel A C Hutton I Tocainide blood levels in patients following intravenous and oral administration (In press)
13 Ryan M Lown B Horn H Comparison of ventricular ectopic activity during 24 hour monitoring and exercise testing in patients with coronary heart disease N Engl J Med 292 224 9 1975
14 MacFarlane I W Lawrie TDV An introduction to automated electrocardiography interpretation London 1974 Butterworth & Co., Ltd
15 Taylor PT Computer analysis of cardiac arrhythmias Ph D thesis University of Glasgow 1974
16 Moller M Reliability of quantitative analysis of ambulatory E C G tape recordings Extract from the Transactions of the European Society of Cardiology 1 1 19 8
17 McLeod A Kitson D McComish M Jewitt D Role of ambulatory electrocardiographic monitoring Accuracy of quantitative analysis system Br Heart J 39 347 1977
18 Rosenbaum MB Chiale PA Halpern MS Nau GJ Przybylski J Levi RJ Lazzari JO Elizari MV Clinical efficacy of amiodarone as an antiarrhythmic drug Am J Cardiol 38 934-44 1976
19 Vismara LA Mason DT Amsterdam EA Disopyramide phosphate Clinical efficacy of a new oral antiarrhythmic drug Clin Pharmacol Ther 16 330-5 1974
20 Podrid PJ Schoenberger A Lown B Congestive cardiac failure caused by oral disopyramide N Eng J Med 302 614 17 1980
21 Chew CY Collett J Singh B N Mexiletine A review of its pharmacological properties and therapeutic efficacy in arrhythmias Drugs 17 161 81 1979
22 Chamberlain DA Oral mexiletine in high risk patients after acute myocardial infarction Proceedings of the Eighth European Congress of Cardiology 9654 p 917
23 Campbell NI Pantridge JF Adgey AA Long team oral anti arrhythmic thearpy with mexiletine Brit Heart J 40 796-804 1978

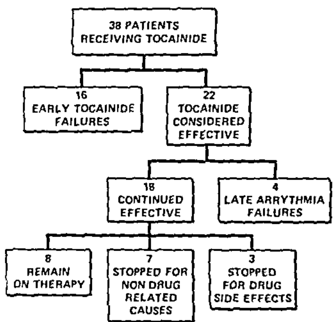


Fig 1 Outcome in 38 patients with ventricular arrhythmias treated with tocainide

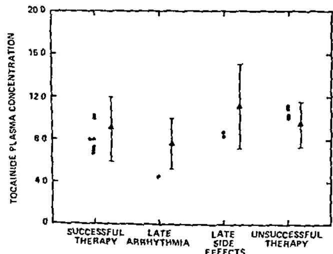


Fig 2 Mean tocainide plasma concentration over one dosing interval. Most patients plasma concentrations were between 6 and 12 μg/ml There was no significant difference between the plasma concentrations in those treated successfully and those treated unsuccessfully

dosage was gradually increased until arrhythmias were controlled or side effects occurred Frequent blood sampling was performed and plasma concentrations[13] given for each patient represent an estimate of the average over a dosing interval

For each patient assessment was made as to the responsiveness of the arrhythmias to lidocaine Comparison between the success or failure of tocainide in patients responsive or nonresponsive to lidocaine was performed by means of the Fisher exact test

Table 1 Response to lidocaine for predicting tocainide success

Tocainide	*Lidocaine effective*	*Lidocaine ineffective*	*Lidocaine not evaluated*
Effective	16	1	1
Ineffective	10	3	7
No effective/ total	16/26 (63%)	1/4 (25%)	1/8 (1[illegible]%)

Results

Patient population There were 38 patients (23 male 15 female) receiving tocainide the average age was 58 ± 12 years Twenty one had coronary disease seven had prior valve replacement, four had mitral valve prolapse three had a cardiomyopathy and three had an otherwise normal heart Congestive heart failure played a prominent role in the prior clinical course of 16 patients

The arrhythmia was sustained ventricular tachycardia and/or fibrillation requiring pharmacologic or electrical conversion in 31 patients Twenty eight patients had experienced more than one episode and 29 had a prior cardioversion In seven patients the arrhythmia was symptomatic ventricular ectopy

Thirty six patients had been treated unsuccessfully with quinidine (average daily dose of 1 5 ± 0 44 gm) 33 with procainamide (2 9 ± 1 1 gm) 28 with propranolol (140 ± 101 mg) and 11 with disopyramide (675 ± 324 mg)

Results of tocainide therapy The results of tocainide therapy are shown in Fig 1 Tocainide therapy was initially effective in 22 of the 38 patients (61%) Four had late arrhythmia recurrences including two who died of ventricular fibrillation after 3½ and 4 months of therapy Eighteen patients had their arrhythmias treated continuously and successfully with tocainide Three of these required discontinuation of the drug after 6 7 and 27 months because of side effects (see below) The remaining 15 patients were treated successfully with tocainide (median duration 13 months) Eight remain on tocainide and in seven it was discontinued for nondrug related causes (One had a spontaneous decline in arrhythmias two died after coronary bypass sur

Open clinical studies at a referral center Chronic maintenance tocainide therapy in patients with recurrent sustained ventricular tachycardia refractory to conventional antiarrhythmic agents

James D Maloney M D Roger G Nissen M D and J M McColgan B S *Rochester Minn*

Chronic maintenance tocainide therapy was effective in controlling symptomatic recurrent ventricular tachycardia in 11 of 15 patients Patients were selected for tocainide therapy on the basis of refractoriness to conventional antiarrhythmic agents and responsiveness to the intravenous administration of lidocaine Side effects were frequent but could usually be managed by taking the drug with meals or by more frequent administration of smaller doses Survival frequency of symptomatic tachycardia frequency of asymptomatic ventricular tachycardia and tolerance of the therapeutically effective dosage were the criteria used to assess therapeutic effectiveness Factors common to the response group included primary and secondary Q T prolongation before therapy a paradoxical increase in ventricular ectopic activity with quinidine like medications and shortening of the Q T interval with maintenance tocainide therapy These factors may prove to be useful in identifying the patients who are most likely to benefit from chronic maintenance tocainide therapy

During the last 400 years the science of medicine has evolved through the use of descriptive analysis experimental investigation modern mathematics and technologic advances The value of descriptive analysis is exemplified by Withering s report in 1785[1] on the use of foxglove *(Digitalis purpurea)* In the report his observations of 10 years on drug preparation dose effect and adverse reactions were analyzed Withering cautioned his readers that no general deductions decisive upon the failure or success of the medicine can be drawn from the cases I now present I wish the reader to keep in view that it is not my intention merely to introduce a new diuretic to his acquaintance but one which though not infallible I believe to be [of] use After all in spite of opinion prejudice or error TIME will fix the real value upon this discovery

The importance of these clinical observations persists today The reasons for initiating therapeutic trials are to confirm the useful properties of a drug device or procedure to define the adverse side effects and to provide a potentially effective intervention for patients with disabling conditions that are refractory to all available therapy[2] In keeping with these goals our experience with tocainide a lidocaine analogue obtained through an emergency open clinical study for patients with refractory ventricular tachycardia is presented

From the Divisions of Cardiovascular Diseases and Internal Medicine and of Pediatric Cardiology Mayo Clinic and Mayo Foundation Rochester Minn

Reprint requests J D Maloney M D 200 First St S W Mayo Clinic, Rochester MN 55901

Selection of patients

From June 1977 to April 1980 seventy eight patients hospitalized at our institution with symptomatic recurrent ventricular tachycardia

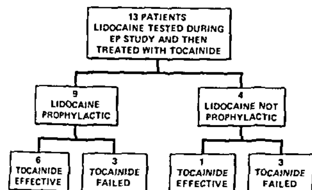


Fig 3 Outcome in 13 patients in whom lidocaine was tested for protection against ventricular tachycardia induced during intracardiac electrophysiologic study Although the acute response to lidocaine was fairly predictive of the long term success or failure of tocainide the correlation was imperfect

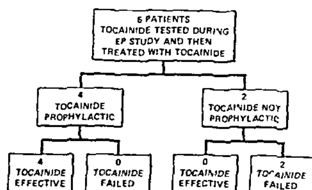


Fig 4 Outcome in six patients undergoing a repeat electrophysiologic study to evaluate ventricular tachycardia inducibility on oral tocainide Although the number of patient is small there was a perfect correlation between the outcome of the electrophysiology study and long term therapy

gery was performed for angina one died of lung carcinoma and three died of heart failure)

Sixteen patients failed to have their arrhythmia controlled with tocainide despite maximally tolerated doses of tocainide The median duration of treatment in these patients was 7 days

Dose and plasma concentration The total daily dose of tocainide ranged from 600 to 2 400 mg daily There was no difference between the daily dose of those treated effectively (1 528 ± 379 mg/day) as compared to those treated ineffectively (1 514 ± 412 mg/day) There was no difference between the plasma concentration for those responding to tocainide (8.9 ± 3.1 gm/ml) and those not responding (9.4 ± 2.2 μg/ml) (Fig 2)

Lidocaine responsiveness for predicting tocainide success Since many of these patients were referred because their arrhythmia was responsive to lidocaine we evaluated the value of a good lidocaine response for predicting the success of tocainide Table I summarizes the results Tocainide therapy was successful in 63% of patients in whom lidocaine was considered effective Tocainide was successful in only two (17%) of the other 12 patients in whom lidocaine was ineffective or in whom it was not evaluated The difference between these groups is statistically significant ($P < 0.02$)

There were 13 patients in whom lidocaine was tested during an electrophysiologic study (Fig 3) Lidocaine protected against induced ventricular tachycardia in 9 of these 13 Six of these nine had successful oral tocainide therapy Lidocaine did not protect against ventricular tachycardia in four patients In three of these patients tocainide therapy was a failure Of six patients in whom oral tocainide was tested during a second electrophysiologic study (Fig 4) four were treated successfully Both patients for whom tocainide was not prophylactic at the time of electrophysiologic study had subsequent spontaneous recurrences of ventricular arrhythmias Lidocaine responsiveness during the electrophysiologic study may aid in selecting patients for oral tocainide therapy However all patients should be retested with tocainide prior to hospital discharge

Side effects Two thirds of patients had side effects (Table II) Side effects occurring during chronic oral therapy tended to be infrequent and were usually not a serious limitation to tocainide therapy Tremor was minimized by taking the drug with food

Three patients had severe side effects during long term therapy and required discontinuation of tocainide One had a prior history of idiopathic and procainamide induced pericarditis Tocainide was stopped after 7 months because of anemia fever and pericarditis Another developed severe arthralgias and arthritis involving the hands after 4 months of therapy which resolved when tocainide was discontinued There was a slight rise in the antinuclear antibody titer This patient had undergone a brief treatment with procainamide 2 months earlier The third patient had an immunologic side effect that seemed best attributed to tocainide After 27 months the patient presented with gross hematuria and had a rise in creatinine

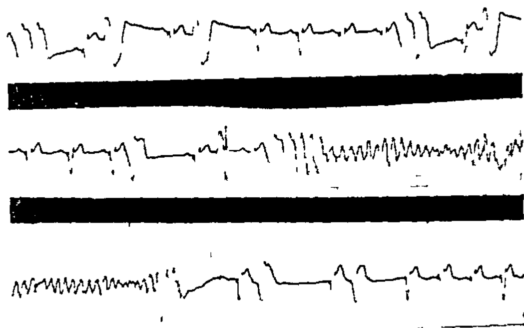


Fig 1 Case 1 Continuous monitoring strip recording of ventricular flutter occurring after second open heart surgery and use of quinidine sulfate

refractory or intolerant to conventional therapy (quinidine procainamide disopyramide propranolol and digitalis—alone or in combination) entered open clinical trials of investigational drugs devices or procedures Seventeen of these patients were managed with cardiac surgical procedures guided by epicardial and intramural electrophysiologic mapping techniques[5] Nine patients received investigational pacing devices for burst ventricular overdrive conversion[6] or dual chamber atrioventricular sequential pacing for control and prevention of ventricular tachycardia associated with intermittent symptomatic bradycardia Fifty seven patients participated in open clinical drug trials of mexiletine verapamil aprindine or tocainide[9] Assignment of an individual patient to a specific drug trial was determined on the basis of the underlying myocardial disease the electrophysiologic characteristics of the tachycardia and the clinical judgment of the attending physician Five patients participated in more than one of the clinical trials Fifteen patients entered the tocainide drug trial and provide the data for this report

Material and methods

Definitions An open clinical study (trial)[1] is defined as a clinical experiment with an investigational drug device or procedure which is applied to achieve a specific outcome and which is known to the patient and to the physician A control or comparison group attained through randomization techniques and the administration of placebo agents are excluded

Ventricular tachycardia is paroxysmal wide complex tachycardia that fulfills the standard electrocardiographic or electrophysiologic (or both) criteria[11]

Chronic recurrent ventricular tachycardia is symtomatic ventricular tachycardia that is documented two or more times and occurs in the absence of an acutely evolving process such as recent myocardial infarction

Sustained paroxysmal ventricular tachycardia is tachycardia lasting for more than 30 seconds or requiring emergency treatment because of hemodynamic collapse or progression to ventricular fibrillation

Torsade de pointes[1] is a variant of rapid ventricular tachycardia which has a surface ECG pattern characterized as a screwlike pattern (rhythmically changing polarity of the QRS deflection as if the sequence of depolarization were turning about the point)

Q T prolongation[13,14] is defined as Q T and Q T intervals obtained from the standard elec

Table II Tocainide side effects

Side effects	*Dose finding (N = 38)*	*Chronic therapy (N = 24)*
Tremor	16 (42%)	10 (42%)
Nausea	9 (24%)	1 (4%)
Anxiety	3 (8%)	0 (0%)
Rash	2 (5%)	1 (4%)
Dizziness	2 (5%)	0 (0%)
Decreased mental status	2 (5%)	0 (0%)
Diaphoresis	1 (3%)	3 (12%)
Ataxia	1 (3%)	3 (12%)
Lightheadedness	1 (3%)	1 (4%)
Menthol on lips	1 (3%)	0 (0%)
Nystagmus	1 (3%)	0 (0%)
Increased arrhythmias	1 (3%)	0 (0%)
Visual problems	1 (3%)	1 (4%)
Fatigue	1 (3%)	0 (0%)
Constipation	0 (0%)	1 (4%)
Hot and cold flashes	0 (0%)	3 (12%)
Nightmares	0 (0%)	1 (4%)
Pericarditis	0 (0%)	1 (4%)
Arthritis	0 (0%)	1 (4%)
Glomerulonephritis	0 (0%)	1 (4%)

to 2 7 mg/dl A renal biopsy showed an immune complex glomerulonephritis This was a nonmembranous glomerulonephritis with immune complex deposition in both the mesangium and the basement membranes Immunofluorescent staining was positive for IgG IgM IgA and C 3 was deposited in a granular pattern (Fig 5) There was no rise in antinuclear antibody titers and antibodies to native DNA were negative With drawal from tocainide resulted in a gradual improvement in renal status

Discussion

This report summarizes our experience with tocainide in a group of patients with severe and life threatening ventricular arrhythmias difficult to manage with standard antiarrhythmic drugs Conclusions from such studies must be made with caution It is difficult to standardize therapy and to make carefully controlled observations with regard to efficacy and side effects Nonetheless our data suggest that tocainide is a valuable antiarrhythmic drug for the management of such patients

This study suggests a reasonable correlation between responsiveness to lidocaine and successful outcome of tocainide therapy An important unanswered question is the tocainide response rate of patients not preselected because of lidocaine responsiveness Only one of eight patients in whom the lidocaine responsiveness status was unknown responded to tocainide In our study the apparent success of tocainide may in large part be due to the fact that patients were preselected because of their lidocaine responsiveness Nonetheless the availability of oral tocainide for patients responsive to lidocaine does represent a valuable addition to our list of antiarrhythmic drugs

Our data suggest that testing intravenous lidocaine in the electrophysiology laboratory[1] can be of value for selecting patients who have a high likelihood of arrhythmia control with tocainide All patients who respond to lidocaine in the electrophysiology laboratory should undergo subsequent electrophysiologic testing on oral tocainide

The range of plasma concentrations associated with excellent arrhythmia control for tocainide was generally from 6 to 12 μg/ml The plasma concentrations associated with side effects were probably only marginally higher than the therapeutic range since many patients were treated with doses just below those associated with side effects For most patients the dose was 400 500 or 600 mg every 8 hours The doses and plasma concentrations for those patients failing tocainide were in the same range as those in patients who had a good response In this study drug plasma concentrations were measured only in retrospect and did not play any role in the management of the patients For these critically ill patients we preferred to increase the tocainide dose to the point where side effects developed and then diminish it slightly Such a practice is reasonable with tocainide since the side effects occurring when patients are under careful observation are minor and resolve promptly and there seems to be little danger of creating serious conduction disturbances or potentially lethal arrhythmias

Although side effects occurred in two thirds of the patients they required drug discontinuation in less than 10% of patients The commonest side effect was a slight tremor most often noted in the upper extremities Nausea was the second most common side effect The three patients requiring discontinuation during long term therapy all experienced immunologic side effects In two of the three it was not certain that tocainide was the

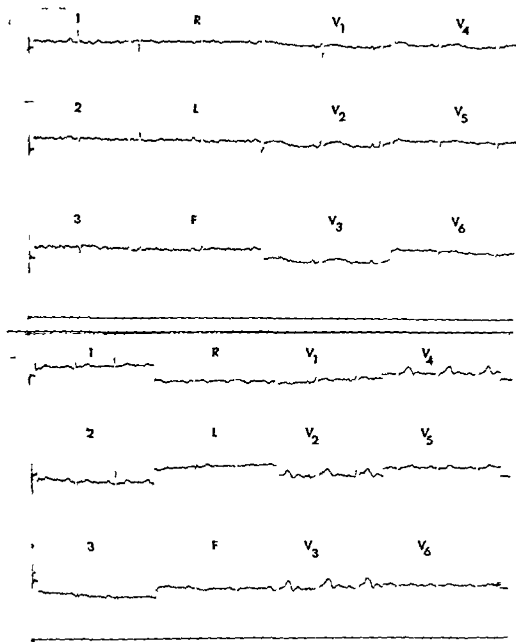


Fig 2 Case 10 *Top* Electrocardiogram recorded 8 days after cardiac arrest (April 8 1978) Pronounced repolarization abnormalities and prolonged Q T intervals are present *Bottom* Electrocardiogram recorded while patient was receiving 2 400 mg tocainide/day (May 9 1978) Repolarization abnormalities and prolonged Q T intervals have improved

trocardiograms and vectorcardiograms which are 10 msec or more beyond the upper limits of normal for age sex and cycle length

Quinidine like medications include quinidine procainamide and disopyramide—antiarrhythmic agents that have membrane stabilizing properties combined with prolongation of the action potential duration

Protocol design and entry criteria All patients entering the emergency open clinical study were hospitalized at our institution for the diagnosis and treatment of recurrent symptomatic ventricular tachycardia or ventricular fibrillation and associated heart disease All but two of the patients were referred from other medical facilities because of therapeutic unresponsiveness The

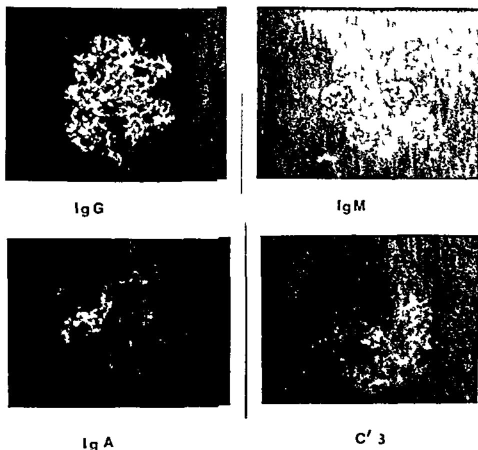


Fig 5 Immunofluorescent stains from renal biopsy of the patient who developed glomerulonephritis There is an irregular lumpy bumpy pattern of immune complex deposition in the glomerulus

precipitating factor One patient had immune complex glomerulonephritis without a rise in the antinuclear antibody titer suggesting that the antibodies formed may not cross react with nuclear proteins

One potential advantage of tocainide may be its minimal arrhythmogenic potential Although one patient in our series may have had ventricular irritability increased by tocainide the drug seemed remarkably free of aggravation of serious arrhythmias Tocainide slightly diminishes the right ventricular effective refractory period and has no significant effect on Q T interval It would not be expected to cause the usual type of drug induced *torsade de pointe* Although many of our patients had severe heart failure the drug was well tolerated However the hemodynamic effects of tocainide after oral therapy have not been well studied and the drug should be used with caution in patients with uncontrolled heart failure We did not observe worsening of conduction disturbances but caution should be exercised in patients with severe conduction abnormalities

In summary tocainide is a useful addition to the group of drugs available to treat severe refractory ventricular arrhythmias We had a reasonable success rate in a group of patients predominantly selected for tocainide because of known responsiveness to lidocaine Further studies will be required to evaluate the drug s effect in less critically ill patients in patients not necessarily responsive to lidocaine and in those who have been treated successfully with other antiarrhythmic drugs The drug requires careful individual patient titration to achieve optimal antiarrhythmic effect and to minimize the occurrence of side effects Most side effects are mild and respond to minor dose adjustments Occasionally the drug must be discontinued because of immunologic side effects during long term therapy

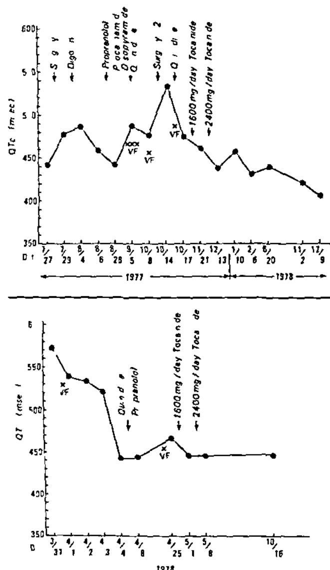


Fig 3 Time course change in corrected Q T intervals. Q T intervals were computed from Bazett s formula Q T = Q T ÷ $\sqrt{RR}$ *Top* Case 1 Q T intervals remained near normal during 1979 and 1980 and the patient has been free of recurrent ventricular tachycardia–ventricular fibrillation *Bottom* Case 10 Q T intervals have remained in normal range throughout 1979 and 1980 and the patient has been free of ventricular tachycardia–ventricular fibrillation

diagnosis of symptomatic refractory recurrent sustained ventricular tachycardia was accepted when (1) ECG or intracardiac electrophysiologic (or both) recordings confirmed the arrhythmia diagnosis and (2) near maximal amounts of commonly available antiarrhythmic agents alone or in combination were unsuccessful in preventing spontaneously occurring sustained ventricular tachycardia or ventricular fibrillation Plasma drug levels were used for determining unresponsiveness and patient compliance If the clinical history referral hospital records or plasma drug levels corroborated unresponsiveness or intoler ance the same therapeutic trial was not routinely repeated When the arrhythmia diagnosis was uncertain and the response to a specific antiar rhythmic therapy difficult to assess His bundle recordings combined with programmed ventricu lar stimulation or other provocative testing tech niques were used to evaluate the patient s statu Serial ventricular stimulation studies were use to assess the therapeutic effectiveness in thos patients with reliably induced and terminate ventricular tachycardia [13]

Refractoriness to conventional antiarrhythmi agents combined with responsiveness to intrave nously administered lidocaine was required (each patient before entry into the clinical tria All participants were informed of the experimen tal nature of tocainide and gave written conser prior to entry The therapeutic goals for eac patient were predefined and included (1) surviva (2) prevention of recurrent sustained ventricula tachycardia and associated hemodynamic co lapse (3) prevention of spontaneously occurrin sustained and nonsustained ventricular tachyca dia and (4) attainment of a satisfactory balanc between control of ventricular tachycardia an unacceptable adverse reactions to tocainide

Results

Characteristics of patients All 15 patients ha well documented recurrent ventricular tachyca dia before entering the open clinical trial Th duration of symptoms before referral ranged fro 2 months to 6 years The ages of the 15 patien (10 males and 5 females) ranged from 9 to years Oral tocainide therapy was maintaine from 4 days to 34 months All patients who we responsive and tolerant to tocainide were chronic maintenance therapy for more than months Eleven of the 15 patients continued chronic maintenance therapy Five patients ha been withdrawn from the study (unresponsiv one patient intolerant three patients responsi and tolerant but withdrawn at aortic valve pro thesis replacement one patient) Three of the five patients have died two with document ventricular tachycardia–ventricular fibrillatio None of the patients has died while on tocaini therapy

The most frequent cause of the underlyi heart disease in this patient group was corona heart disease with previous myocardial infarctio

REFERENCES

1 Coltart DJ Berndt TB Kernoff R Harrison DC Antiarrhythmic and circulatory effects of Astra W3609, a new lidocaine like agent Am J Cardiol 34 35 1974
2 Winkle RA Meffin PJ Fitzgerald JW Harrison DC Clinical efficacy and pharmacokinetics of a new orally effective antiarrhythmic tocainide Circulation 54 884 1976
3 Winkle RA Meffin PJ Harrison DC Long term tocainide therapy for ventricular arrhythmias Circulation 57 1008 1978
4 Woosley RL McDevitt DG Nies AS Smith RF Wilkinson GR Oates JA Suppression of ventricular ectopic depolarizations by tocainide Circulation 56 980 1977
5 McDevitt DG Nies AS Wilkinson GR Smith RF Woosley RL Oates JA Antiarrhythmic effects of a lidocaine congener tocainide 2 amino 2 6 propionoxylidide in man Clin Pharmacol Ther 19 396 1976
6 Engler R Ryan W LeWinter M Bluestein H Karliner JS Assessment of long term antiarrhythmic therapy Studies on the long term efficacy and toxicity of tocainide Am J Cardiol 43 612 1979
7 Lalka D Meyer MB Duce BR Elvin AT Kinetics of the oral antiarrhythmic lidocaine congener tocainide Clin Pharmacol Ther 19 757 1976
8 Meffin PJ Winkle RA Blaschke TF Fitzgerald J Harrison DC Response optimization of drug dosage Antiarrhythmic studies with tocainide Clin Pharmacol Ther 22 42 1977
9 Anderson JL, Mason JW Winkle RA Meffin PJ Fowles RE Peters F Harrison DC Clinical electrophysiologic effects of tocainide Circulation 57 685 1978
10 Moore EN Spear JF Horowitz LN Feldman HS Moller RA Electrophysiologic properties of a new antiarrhythmic drug—tocainide Am J Cardiol 41 03 1978
11 Schnittger I Griffin JC Hall RJ Meffin PJ Winkle RA Effects of tocainide on ventricular fibrillation threshold, comparison with lidocaine Am J Cardiol 42 76 1978
12 Winkle RA Anderson JL, Peters F Meffin PJ Fowles RE Harrison DC The hemodynamic effects of intravenous tocainide in patients with heart disease Circulation 57 787 1978
13 Meffin PJ Harapat SR Harrison DC High pressure liquid chromatographic analysis of drugs in biological fluids II Determination of an antiarrhythmic drug, tocainide as its dansyl derivative using a fluorescence detector J Pharm Sci 66 583 1977
14 Mason JW Winkle RA Electrode catheter arrhythmia induction in the selection and assessment of antiarrhythmic drug therapy for recurrent ventricular tachycardia Circulation 58 971 1978

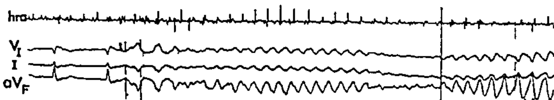


Fig 4 Case 1 Ventricular flutter with shifting axis *(torsade de pointes)* induced by paired ventricular extrastimuli at S S intervals of 220 to 250 ms while patient was receiving 1 600 mg tocainide/day Note atrial fibrillation previously induced by rapid atrial pacing hra = high right atrial electrogram Other intracardiac recordings have been omitted V I and aV are standard ECG leads

Four of the six patients with this condition have withdrawn from the study Five patients had primary myocardial disease presenting as congestive cardiomyopathy Two patients had generalized ventricular dilatation and hypokinesis one after surgical replacement of an aortic valve prosthesis and the other after revision of a ventricular-pulmonary artery conduit and residual ventricular septal defect[1] One patient had normal ventricular function and chronic active myocarditis diagnosed on the basis of findings on serial right ventricular biopsy specimens and cardiac catheterization One patient had recurrent ventricular tachycardia in the absence of clinically detectable heart disease

Invasive hemodynamic and angiographic data of recent cardiac catheterizations were available for 13 of the 15 patients Thirteen patients were in New York Heart Association Functional Class III or IV for dyspnea Ten patients had cardiomegaly and 11 patients required chronic maintenance digitalis therapy for congestive heart failure Twelve of the patients had been successfully resuscitated and defibrillated on two or more occasions Six patients had had previous open heart surgical procedures

Seven patients had histories of quinidine induced syncope[7] or a paradoxical increase in ventricular ectopic activity while taking quinidine and quinidine like drugs (Fig 1) In one of these seven patients the administration of quinidine procainamide and disopyramide consecutively produced spontaneously occurring ventricular tachycardia and ventricular fibrillation Although ventricular ectopy was frequent in all seven patients ventricular fibrillation had not occurred in the absence of these drugs Electrocardiograms demonstrated Q T prolongation in 11 patients The Q T prolongation was unrelated to identifiable factors in five patients and was secondary to quinidine like drugs in six patients Diffuse repolarization abnormalities presenting as prominent U waves were common The prolonged Q T intervals decreased during tocainide therapy (Fig 2) Ventricular fibrillation was most likely to develop when the Q T intervals were prolonged because of myocardial injury or drugs (Fig 3)

His bundle electrocardiography combined with programmed ventricular stimulation studies was performed in 10 patients Sustained ventricular tachycardia could be induced and terminated in seven however in four patients the tachycardia was rapid hemodynamically unstable and had a shifting electrical axis on the surface electrocardiogram consistent with the atypical ventricular tachycardia *torsade de pointes* (Fig 4) and required emergency cardioversion A similar type of ventricular tachycardia-ventricular fibrillation occurred in a 9 year old child receiving tocainide alone The episode of atypical ventricular tachycardia was precipitated by burst exercise and terminated spontaneously several seconds after the child collapsed The addition of propranolol (20 mg four times a day) to tocainide decreased exercise induced ectopy and prevented further ventricular fibrillation

Maintenance tocainide therapy ranged from 600 to 3 200 mg daily (1 200 to 3,200 mg daily for adults) The daily maintenance dose was determined by increasing the dosage every 2 to 3 days until the predefined therapeutic goals were achieved or until adverse side effects necessitated a decrease in dosage Steady state plasma concentrations were not immediately available On retrospective review effective plasma concentrations ranged from 5 to 19 μg/ml Blood levels higher than 13 μg and daily tocainide doses higher than 2 400 mg were usually intolerable

Drug tolerance and side effects No patient was completely free of side effects during the

.fety evaluatıon of tocaınide ın the American ıergency Use Program

ﾑard R Horn M D Zareh Hadıdian Ph D Jeanne L Johnson
Helen G Vassallo Ph D John H Williams M D and Michael
Young M D Ph D *Framıngham Mass*

ıs a report of the safety evaluation of tocaınide in the first 369 patients entered into the American nide Emergency Use Program This humanitarian protocol has made tocainide available for ıergency use in the treatment of l fe threatening intractable ventricular arrhythm as in patients who vere *unresponsive to or unable to take the approved antiarrhythmic drugs The most frequent adverse* xperiences reported were neurolog c and gastro ntestinal in nature and included dizz ness ghtheadedness tremors nausea vomiting and anorexia Adverse experiences resulted in the scontinuation of tocainide in 16 / of these patients and were transient and revers ble with no onclusive evidence of permanent organ injury Adverse experiences having special relevance to the ıfety assessment of new antiarrhythmic agents are discussed includ ng congestive heart failure rrhythm as and conduction disturbances convulsions lupus erythematosus like illness and deaths wh le n therapy No significant abnormal trends were observed in routine hematolog c and biochemical ıboratory screen ng tests or in ophthalmolog c or chest x-ray exam nations An evaluation of the effects l chronic tocainide adm nistration on ECG intervals showed no s gnificant change in P R or QRS ıtervals but demonstrated a statistically sign f cant decrease in Q T duration It is concluded that n atients with life-threatening ventricular arrhythmias tocainide is a safe agent with a favorable risk enefit ratio

?ocaınide a new lidocaine like oral antiarrhyth nic agent has been studied extensively in ılanned protocols [1-4] In addition this membrane ıctive agent has been available since 1974 for ·mergency use in patients with intractable ven ricular arrhythmias Consequently the Ameri :an Tocainide Emergency Use Program has pro ıided a unique opportunity to evaluate the safety ıf tocainide in seriously ill patients treated with he drug for periods up to 41 5 months The first 369 patients admitted to the program between November 30 1974 and September 30 1978 are he subject of this report These patients entered :he protocol in response to requests by their physicians who had reached an impasse in the management of their life threatening refractory ventricular arrhythmias Over 200 practicing physicians participated in the program as investiga tors during this 4 year period

The criteria for entering the program were that the ventricular arrhythmias were considered to be life threatening and the patients were unrespon sive to or were unable to take (intolerance or contraindication) the approved antiarrhythmic drugs quinidine procainamide propranolol and subsequently disopyramide

Upon entry into the protocol, 60% of these patients were in New York Heart Association Class III or IV demonstrating respectively mod erate or severe compromise of cardiac status Seventy one (19%) patients were treated with tocainide for over 1 year 51 (14%) for 6 to 12 months, and 107 (29%) for 1 to 6 months

Clinical parameters in safety assessment

Most frequent adverse experiences reported In a long term open label open-ended study of patients with severe underlying heart disease

From Astra Pharmaceutical Products, I c Framingham Mass.
Reprint requests How rd R. Horn, M.D Astr Pharmaceutical Produ ts, Inc P O Bo 1089 Framingham MA 01701

Table I Outcomes of maintenance tocainide treatment in 11 patients with refractory ventricular tachycardia

Therapy goals	*No of patients*
Tolerance of effective dosage	11
Survival while taking tocainide	15†‡
Survival and tolerance	10†‡
Prevention of	
VT with syncope or shock	9
Symptomatic VT	7
Asymptomatic VT	5

Patients tolerated therapy for > 2 mo four other patients withdrew from trials at 4 8 9 and 31 days.

†One patient withdrew from trial at 21 months for surgery died of left ventricular failure after valve replacement

‡Three patients (all in the group that withdrew) died two died of ventricular tachycardia ventricular fibrillation

entire treatment period in part because of the dosing technique and the patient population Although pharmacokinetic studies suggest that dosing intervals every 8 to 12 hours should result in maintenance of adequate blood levels for suppression of ventricular ectopy we found that 6 hour dose intervals were more effective in suppressing malignant arrhythmias while minimizing dose related side effects Four patients required drug administration five to six times per day in order to achieve tolerance Mild side effects of the central nervous system were experienced by all patients Ten of the patients complained of mild to severe nausea Vomiting was infrequent Gastrointestinal intolerance and a diffuse skin rash developed in three patients during the first week of therapy and these side effects necessitated the subsequent withdrawal of the three patients from the drug trial on days 7 8 and 31 respectively One additional patient developed a mild rash that was managed by temporary dose reduction In addition to dizziness tremulousness and paresthesias a common side effect of the central nervous system consisted of memory loss and a decreased ability to work with numbers Although there was a wide variation among individual patients the presence and severity of most side effects were closely related to the size of each individual dose and the total daily dose In general side effects decreased with time and could be reduced by either taking the drug with meals or taking it more frequently

Drug efficacy Thirteen of the patients had a favorable response with tocainide alone or in combination In one patient the combination of tocainide and propranolol was effective whereas tocainide alone was associated with increased ventricular ectopy The one patient who was withdrawn from the study at 4 days because of unresponsiveness had paroxysmal ventricular tachycardia associated with acute coronary insufficiency The arrhythmia was no longer refractory to lidocaine analogues after saphenous vein bypass surgery None of the patients died while receiving maintenance tocainide therapy whereas three of the five patients withdrawn from the drug trial because of intolerance died

Drug efficacy as determined by the predefined therapeutic goals is summarized in Table I Two patients had syncope secondary to paroxysmal sustained ventricular tachycardia–ventricular fibrillation Both patients had omitted one or two medication doses just before the episode Both patients required hospitalization and were successfully managed Prolonged ECG monitoring obtained during rehospitalization and through periodic ambulatory ECG monitoring demonstrated a decrease in sustained and nonsustained ventricular tachycardia Partial or total tocainide withdrawal during follow up hospitalizations resulted in an increase in ventricular ectopic activity in seven patients Eight patients have had improvement in their exercise tolerance and have less exertional dyspnea A clinically significant negative inotropic effect of tocainide has not been observed Seven patients have had reassessment of left ventricular function by echocardiography radioisotope imaging or catheterization techniques during the follow up period Comparisons of cardiac index wall motion chamber size and left ventricular end diastolic pressure also suggest that tocainide is well tolerated hemodynamically even when used for patients with poor left ventricular function

Discussion

Life threatening ventricular arrhythmias remain a therapeutic challenge The currently available antiarrhythmic agents are often ineffective or are not tolerated because of adverse side effects Occasionally these agents will increase ventricular ectopy and the vulnerability to ventricular fibrillation When patients with symptomatic or asymptomatic ventricular tachyarrhythmias are being treated the implied thera

Table I Percentage occurrence of most frequent adverse experiences in 369 patients treated with tocainide

Adverse experience	*% of patients*
Gastrointestinal	
Nausea	34
Vomiting	16
Anorexia	15
Central nervous system	
Dizziness	31
Lightheadedness	24
Tremors	22
Paresthesias	16
Confusion	15
Nervousness	13
Other	
Palpitations	17
Shortness of breath	13
Rash	12

associated with life threatening refractory ventricular arrhythmias one should anticipate the reporting of a number of adverse experiences because of the long duration of exposure to a variety of factors This was the case in the Emergency Use Program as most patients reported one or more adverse experiences at some point during the entire period of treatment Table I shows the percentage occurrence of the most frequent adverse experiences in the 369 patients in this study The sources of data for this table include not only documented information from the conventional investigator s data form but also all other available information some of which may be considered undocumented The latter sources include hospital and office charts physician s and nurse s notes physician s correspondence and reports of the sponsor s site visits and telephone contacts Patients were included in this table if an adverse experience occurred only once during the entire period of treatment The majority of reported adverse experiences were neurologic or gastrointestinal in nature The neurologic experiences appeared to be related to dosing indicating a possible relation to peak blood levels and penetration of the blood brain barrier such as occurs with lidocaine Although these mostly subjective experiences were sometimes distressful for the patients they were usually transient in nature and reversible with no evidence of permanent organ injury

Adverse experiences resulting in discontinuation of tocainide The adverse experiences of greatest importance were those severe enough to result in the discontinuation of tocainide therapy This occurred in 60 (16%) of the patients in the program The frequency distribution of these adverse experiences is provided in Table II Only rarely was a causal relationship between tocainide and the adverse experience tested by a rechallenge with tocainide In dealing with severely ill patients it is difficult to establish cause and effect relationships for any drug and particularly difficult for an antiarrhythmic agent Neurologic and gastrointestinal adverse experiences were a primary cause of discontinuation in 48 of the 60 dropouts (80%)

Rash was the only adverse experience accounted for four patient discontinuations In two patients recurrence of the rash was observed following rechallenge with tocainide While fever was reported as an adverse experience in only one subject did it subside with discontinuation of tocainide and return with rechallenge One patient was discontinued because of hepatitis confirmed by a liver biopsy that could not distinguish between infection and a drug reaction Cytomegalovirus was suggested as a possible etiologic agent by the investigator Another patient was discontinued because of elevated liver enzymes This patient had aortic valve replacement just prior to starting tocainide and the possibility of a serum hepatitis must be considered One patient was discontinued (after receiving 1 400 mg of tocainide over 24 hours) because of the development of acute pulmonary edema 5 hours after the last dose The patient had a previous left ventricular aneurysmectomy and was in New York Heart Association Functional Class IV Understandably this patient was not rechallenged and other possible inciting factors could not be completely ruled out One patient was discontinued because of the development of polyarthritis and an elevated antinuclear antibody (ANA) titer The investigator stated that other explanations could not be dismissed such as the concurrent treatment with disopyramide and the recently discontinued procainamide One patient was discontinued because of recurrent pericarditis associated with an elevated ANA titer both of which antedated the onset of tocainide therapy One patient developed what appeared on chest x ray films to be an interstitial

peutic goal is to prevent spontaneous sustained ventricular tachycardia-ventricular fibrillation and sudden cardiac death Preventive treatment is based on the assumptions that (1) a reduction in ventricular ectopic activity decreases vulnerability to ventricular tachycardia-ventricular fibrillation and (2) the reduction in ventricular ectopic activity reflects the clinically significant antiarrhythmic properties of the drug in question

Recent studies have challenged these assumptions Frequency of premature ventricular contractions and various grades of ventricular ectopy short of bursts of ventricular tachycardia may have limited predictive value in identifying high risk patients[19] Also the large day to day variability in ventricular ectopy makes attributing the change in frequency of premature ventricular contractions to a specific antiarrhythmic agent hazardous The value of programmed ventricular stimulation techniques in identifying high risk subset patients and defining effective long term antiarrhythmic programs remains uncertain In this setting clinical observations and descriptive analysis over a long period are essential for documentation of clinically significant antiarrhythmic benefits The end points of (1) survival (2) paroxysmal tachycardia with hemodynamic collapse and (3) symptomatic nonsustained ventricular tachycardia can be clearly defined so that conclusions regarding drug efficacy for an individual patient are possible In this highly selected patient group tocainide was therapeutically useful Conclusions regarding antiarrhythmic drug efficacy in a nonselected population should not be drawn from our experience However awareness of several factors common to this group may be useful in identifying patients likely to benefit from tocainide therapy These factors include responsiveness to intravenously administered lidocaine quinidine induced syncope or increasing ventricular ectopy with quinidine like medications primary or secondary Q T prolongation and shortening of the Q T interval with maintenance tocainide therapy

Supporting the importance of prolongation of the Q T interval Haynes et al[3] reported a high incidence of Q T prolongation and repolarization abnormalities in patients surviving out of hospital ventricular fibrillation and also noted the continued high risk for repeat episodes of ventricular fibrillation The association between sudden death and Q T prolongation also has been described for postinfarction patients[7] and for patients with hereditary prolongation of the Q T interval The frequent occurrence of Q T prolongation quinidine induced syncope and *torsade de pointes* may reflect specific electrophysiologic mechanisms that are advantageously modified by tocainide or lidocaine These patients may represent a specific subgroup of patients who are likely to benefit from tocainide therapy Additional investigation is needed to substantiate these relationships

Simultaneous maintenance digitalis and tocainide therapy was used in 11 of our patients without untoward clinical effects or without alterations in expected blood levels Combination antiarrhythmic therapy consisting of propranolol and tocainide or quinidine like drugs and tocainide improved antiarrhythmic control achieved by a single drug in higher concentrations Combination therapy permitted lower dosages and reduced side effects This apparent complementary interaction probably reflects the different electrophysiologic actions of the drugs and emphasizes the potential importance of an oral lidocaine analogue Irreversible side effects were not observed in this series Side effects were common and generally were related to the size of each dose and the total number of milligrams per day Careful titration between drug efficacy and intolerable side effects can be achieved in most patients

This experience suggests that tocainide has a place in the treatment of refractory ventricular tachycardia and that chronic maintenance tocainide therapy may be particularly beneficial for patients who are responsive to intravenously administered lidocaine who present with prolonged Q T intervals and who are unresponsive to quinidine like agents

REFERENCES

1 Withering W An account of the foxglove and some of its medical uses With practical remarks on dropsy and other diseases Birmingham England, 1785 M Swinney
2 Feinstein AR Clinical biostatistics XXVI Medical ethics and the architecture of clinical research Clin Pharmacol Ther 15 316 1974
3 Feinstein AR Clinical biostatistics St Louis 19 7 The CV Mosby Co
4 Murphy EA The logic of medicine Baltimore 1976 Johns Hopkins University Press
5 Allen WB Maloney JD Hartzler GO Holmes DR Jr Puga FJ Resection of ventricular aneurysm modified by electrophysiologic assessment in patients with intracta

pulmonary edema that persisted despite diuretic therapy A lung biopsy was interpreted as showing interstitial pneumonitis This patient was afebrile with no rash or joint symptoms and had a normal white cell count and ANA titer Tocainide was stopped and treatment with corticosteroids begun after which pulmonary function and chest x ray findings improved She was not rechallenged with tocainide and other possible causes were not ruled out

Special adverse experiences in antiarrhythmic therapy In the safety evaluation of a new antiarrhythmic agent there are several adverse experiences of particular importance These include increased congestive heart failure increased ventricular arrhythmia aggravation of preexisting cardiac conduction disturbances convulsions and a lupus erythematosus–like syndrome In the Emergency Program no causal relationship with tocainide to these experiences could be definitely established Even if a causal relationship were established between tocainide and such effects the comparison with conventional antiarrhythmic agents would be most favorable

Table III exhibits these special adverse effects for the 369 Tocainide Emergency Program patients There were five patients in whom the initiation of tocainide therapy was reported to have possibly aggravated severe preexisting heart failure All five patients were in New York Heart Association Functional Class IV before tocainide treatment Three had a diagnosis of cardiomyopathy and two had coronary disease with old myocardial infarction Only one of the patients was discontinued because of this experience and four of the patients were known to subsequently die of heart failure It is of interest that a number of patients who were unable to tolerate disopyramide or propranolol because of heart failure were subsequently able to tolerate tocainide

Only four patients who received an adequate trial of tocainide therapy were stopped because of an alleged increase in ventricular arrhythmia occurring during initiation of therapy Of interest at least eight long term tocainide responders with abolition or substantial reduction of life threatening arrhythmic events while on tocainide had been uncontrolled and had manifested a prolonged Q T interval during prior treatment with quinidine procainamide and disopyramide

There were two patients with preexisting cardiac conduction disturbances that may possibly have been aggravated by tocainide although other explanations exist for the observed conduction changes One patient who exhibited transient second degree A V block was concurrently receiving digoxin and a beta blocker and was continued on tocainide for 36 months without any subsequent conduction problem The other patient had advanced degrees of A V block but had recently undergone mitral valve replacement which may be associated with transient or permanent changes in A V conduction

Convulsions were reported to occur in two patients while on tocainide no other obvious explanation for these convulsions exists Both patients were women over 80 years of age one

Table II Adverse experiences resulting in discontinuation among 369 patients

Adverse experience	*No of patient*
Neurologic	24 (6.5%)
Gastrointestinal	1 (3.2%)
Neurologic/gastrointesinal	11 (3.0%)
Neurologic/sun sensitivity	1 (0.27%)
Neurologic/supraventricular tachycardia	1 (0.2%)
Rash fever neurologic	1 (0.[illegible]%)
Rash	4 (1.1%)
Rash fever hepatitis	1 (0.2%)
Elevated liver enzymes	1 (0.2%)
Increased congestive heart failure	1 (0.2%)
Arthritis	1 (0.[illegible]%)
Recurrent pericarditis	1 (0.[illegible]%)
Interstitial pneumonitis	1 (0.[illegible]%)
Total	60 (16.3%)

Table III Adverse experiences of particular relevance in antiarrhythmic drug therapy

Adverse experiences	*No of possible occurrences in 369 patients*
Increased congestive heart failure during initiation of tocainide therapy	5 (1.4%)
Increase of ventricular arrhythmia during initiation of tocainide	4 (1.1)
Possible aggravation of preexisting cardiac conduction disturbances	2 (0.5%)
Convulsions	2 (0.5%)
Lupus erythematosus–like illness	3 (0.8%)

ble ventricular tachycardia and left ventricular aneurysm (abstract) Am J Cardiol 45 417 1980
6 Hartzler GO Treatment of recurrent ventricular tachycardia by patient activated radiofrequency ventricular stimulation Mayo Clin Proc 54 75 1979
7 Maloney JD Holmes DR Jr Gersh B Broadbent JC Hartzler GO Merideth J Berkovits BV Control conversion and prevention of resistant dysrhythmias with demand and double-demand atrioventricular sequential pacing (abstract) PACE 3 379 1980
8 Zipes DP Troup PJ New antiarrhythmic agents Amiodarone aprindine disopyramide ethmozin mexiletine tocainide verapamil Am J Cardiol 41 1005 1978
9 Solberg LE Nissen RG Vlietstra RE Callahan JA Prinzmetal s variant angina—response to verapamil Mayo Clin Proc 53 256 1978
10 Good CS Clarke C The principles and practice of clinical trials Edinburgh Scotland 1976 Churchill Livingstone
11 Wellens HJJ Duren DR Lie KI Observations on mechanisms of ventricular tachycardia in man Circulation 54 237 1976
12 Krikler DM Curry PVL *Torsade de pointes* an atypical ventricular tachycardia (editorial) Br Heart J 38 117 1976
13 Haynes RE Hallstrom AP Cobb LA Repolarization abnormalities in survivors of out-of hospital ventricular fibrillation Circulation 57 654 1978
14 Schwartz PJ Wolf S QT interval prolongation as predictor of sudden death in patients with myocardial infarction Circulation 57 1074 1978
15 Hartzler GO Maloney JD Programmed ventricular stimulation in management of recurrent ventricular tachycardia Mayo Clin Proc 52 731 1977
16 Rastelli GC Wallace RB Ongley PA Complete repair of transposition of the great arteries with pulmonary stenosis A review and report of a case corrected by using a new surgical technique Circulation 39 83 1969
17 Reynolds EW Vander Ark CR Quinidine syncope and the delayed repolarization syndromes. Mod Concepts Cardiovasc Dis 45 117 1976
18 Ryan W Engler R LeWinter M Karliner JS Efficacy of a new oral agent (tocainide) in the acute treatment of refractory ventricular arrhythmias Am J Cardiol 43 285 1979
19 Fisher JD Ventricular tachycardia—practical and provocative electrophysiology (editorial) Circulation 58 1000 1978

had previous brain damage from multiple cardio pulmonary resuscitations and the other had a tocainide blood level of 20 µg/ml

There were three patients in whom a lupus erythematosus-like illness was reported while on tocainide Two of these were discontinued and had confounding factors preventing the determination of a causal relationship to tocainide The third patient had a prior history of a procainamide induced lupus like illness A myocardial biopsy done before tocainide was started revealed myocarditis and the possibility of a preexisting collagen disease was raised While on tocainide he had intermittent arthralgias rash fever light sensitivity and proteinuria The ANA titer fluctuated between negative and positive for 38 months of continuous tocainide treatment during which the drug was never stopped

Deaths during tocainide therapy Thirty three patients died while on tocainide therapy Of these patients 28 had a diagnosis of coronary artery disease and five had cardiomyopathy Prior to tocainide therapy 58% of the 33 patients were in New York Heart Association Functional Class IV and 85% were in Class III or IV which placed them in a high risk category for death Thirteen of the deaths (39%) were characterized as arrhythmic or sudden Seven patients died of acute myocardial infarction eight patients of progressive heart failure one of a cerebrovascular accident one of a pulmonary embolus one of pneumonia and in two patients the causes were unclear Eleven of the thirteen arrhythmic deaths occurred in patients with a documented history of resuscitation for ventricular fibrillation prior to tocainide therapy In no case did either the patient s physician or the sponsor find conclusive or even strongly suggestive evidence that tocainide caused the death

Laboratory parameters in safety assessment

No significant abnormal trends were detected in the laboratory safety screening data This assessment included periodic measurements of hemoglobin hematocrit red blood cell counts reticulocyte counts white blood cell and differential counts platelet counts blood urea nitrogen creatinine liver function electrolytes Coombs tests ANA titers urinalyses and chest x ray films Routine ophthalmologic examinations detected no specific toxic effect on the eye

Electrocardiography as a parameter of drug safety was the subject of special study The Tocainide Emergency Use Program afforded a unique opportunity to evaluate the effects of long term oral antiarrhythmic therapy on ECG intervals in contrast to protocols in which tocainide was administered orally for only brief periods[1, 2] or intravenously[3, 6] Accordingly an evaluation of P R interval QRS duration and rate corrected Q T interval was performed retrospectively on a group of 43 emergency patients who had received the drug for at least 6 months with a mean of 16 months Chronic tocainide therapy produced no significant change in P R interval or QRS duration but resulted in a statistically significant decrease in QT duration This latter observation may have been due to a tocainide effect or alternatively to the discontinuation of quinidine like drugs just before or during tocainide therapy

Conclusions

Based on this analysis of the first 369 patients in the Tocainide Emergency Program our conclusions are as follow (1) Adverse experiences with tocainide were primarily neurologic and gastrointestinal in nature (2) Adverse experiences were transient and reversible with no conclusive evidence of permanent organ injury (3) Adverse experiences resulted in discontinuation of tocainide in 16% of patients (4) In patients with life threatening ventricular arrhythmias tocainide is a safe agent with a favorable risk benefit ratio

REFERENCES

1 Winkle RA Meffin PJ Fitzgerald JW Harrison DC Clinical efficacy and pharmacokinetics of a new orally effective antiarrhythmic tocainide Circulation 54 884 1976
2 McDevitt DG Nies AS Wilkinson GR Smith RF Woosley RL Oates JA Antiarrhythmic effects of a lidocaine congener tocainide 2 amino 2' 6 propionoxylidide in man Clin Pharmacol Ther 19 396 1976
3 Winkle RA Meffin PJ Harrison DC Long term tocainide therapy for ventricular arrhythmias Circulation 57 1008 1978
4 LeWinter MM Engler RL, Karliner JS Tocainide therapy for treatment of ventricular arrhythmias Assessment with ambulatory electrocardiographic monitoring and treadmill exercise Am J Cardiol 45 1045 1980
5 Anderson JL, Mason JW Winkle RA Meffin PJ Fowles RE Peters F Harrison DC Clinical electrophysiologic effects of tocainide Circulation 57 685 1978
6 Horowitz LN Josephson ME Farshidi F Human electropharmacology of tocainide a lidocaine congener Am J Cardiol 42 276 1978

Repetitive responses to ventricular extrastimuli incidence, mechanism, and significance

Ardeshir Farshidi M D
Eric L Michelson M D *
Allan M Greenspan M D *
Scott R Spielman M D *
Leonard N Horowitz M D *
Mark E Josephson M D ****
Philadelphia Pa

Repetitive ventricular responses are commonly induced by programmed ventricular stimulation The mechanisms and clinical significance of these repetitive responses specifically their relationship to malignant ventricular tachyarrhythmias have not been clarified The present study was designed to (1) determine the incidence of such responses (2) analyze the different types of repetitive ventricular responses and (3) assess their relationship to clinical arrhythmias

Methods and materials

The study population included 400 consecutive patients undergoing electrophysiologic evaluation in whom ventricular stimulation was performed between July 1973 and January 1978 at the Hospital of the University of Pennsylvania Programmed ventricular stimulation was done routinely in all patients undergoing electrophysiologic evaluation of conduction and rhythm disorders This group included 289 patients with organic heart disease and 111 patients with no clinical evidence of heart disease Ischemic heart disease (diagnosed by previous myocardial infarction typical angina pectoris or positive coronary angiography) was the most common underlying organic disease (197 patients) Thirty patients had valvular heart disease 20 had cardiomyopathy 18 had congenital heart disease and the remainder (24) had hypertensive cardiovascular disease No patients in this group were within two weeks of myocardial infarction Fifty eight patients were studied because of documented sustained ventricular tachycardia or ventricular fibrillation All studies were performed in the nonsedated postabsorptive state after informed consent was obtained Antiarrhythmic agents were not administered in the 24 hours prior to study

Three to five electrode catheters were inserted percutaneously through the femoral and/or antecubital veins and were positioned under fluoroscopic control in the right atrium coronary sinus atrioventricular junction for His bundle recording and in the right ventricular apex In 48 patients undergoing evaluation of ventricular tachycardia or ventricular fibrillation an addi

From the Electrophysiology Laboratory Hospital of the University of Pennsylvania, Cardiovascular Section Department of Medicine University of Pennsylvania School of Medicine Philadelphia Pa

Supported in part by grants from the American Heart Association Southeastern Pennsylvania Chapter and National Heart Lung and Blood Institute

Received for publication Jan 23 1979

Accepted for publication May 11 1979

Reprint requests Mark E Josephson M D Director Electrophysiology Laboratory 666 White Building Hospital of the University of Pennsylvania, 3400 Spruce St Philadelphia Pa 19104

* Drs Michelson and Spielman are recipients of National Institutes of Health Institutional Training Grant 1 T32 HL0 346-01

Dr Greenspan is the recipient of National Institutes of Health Grant 1 F32 HL0 816-01

Dr Horowitz is the recipient of Career Development Investigatorship from the American Heart Association Southeastern Pennsylvania Chapter

Dr Josephson is the recipient of a Research Career Development Award from the National Heart Lung and Blood Institute Grant No 1 K04 HL00361-01

0002 8 03/80/070059 + 10$01 00/0 © 1980 The C V Mosby Co

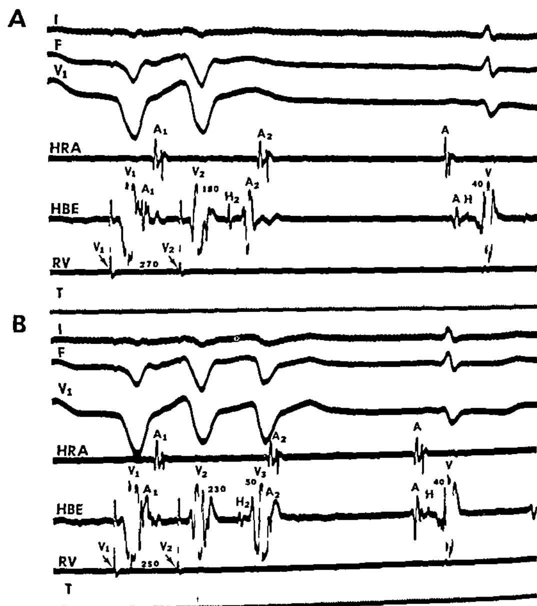


Fig 1 Initiation of bundle branch reentry Surface Leads 1 aVr (F) and V are shown with intracardiac electrograms from the high right atrium (HRA) His bundle recording site (HBE) and right ventricle (RV) In panel A after the eighth complex (V_1) at paced ventricular cycle length of 600 msec a premature ventricular stimulus (V_2) is introduced at a coupling interval of 270 msec Retrograde His Purkinje delay (V_2 H) of 180 msec results In panel B at a shorter coupling interval (V V = 250 msec) a critical degree of V H delay occurs and results in an extra ventricular complex due to bundle branch reentry Note the H V is 50 msec which is slightly longer than the H V during sinus rhythm (40 msec) Note the similarity in morphology between the premature complex and the bundle branch reentrant complex (V) A H V are atrial His bundle and ventricular electrograms, respectively T = time lines

tional electrode catheter was inserted into either the femoral artery percutaneously or into the brachial artery by cutdown and was advanced to the left ventricle for left ventricular recording and/or stimulation Two or three surface electrocardiographic leads and intracardiac electrograms from different sites were displayed on a multichannel oscilloscope (Electronics for Medicine DR 16 White Plains N Y) and were simultaneously recorded on magnetic tape (Honeywell 5600C) Data were subsequently retrieved on photographic paper for analysis at paper speeds of 100 to 200 mm /sec

Ventricular stimulation was performed using a programmable constant current impulse generator (Bloom Associates Ltd Narberth Pa

'eatment of ventricular arrhythmias with al tocainide

chael D Young M D Ph D Zarch Hadidian Ph D
ward R Horn M D Jeanne L Johnson A B and
len G Vassallo Ph D *Framingham Mass*

is a report of a multicenter open study of the use of tocainide a new l docaine like antiarrhythmic a high oral bioava lability in the treatment of l fe threatening ventricular arrhythmias refractory to r therapy The majority of patients have received 1 200 to 2 400 mg daily in divided doses and have treated for over 6 months and some for longer than 3 years Overall 61% of the patients onded successfully to tocainide therapy In the 252 patients with documented severe symptomatic ythmias 71 / responded and the majority (87 /) showed a total abolition of symptomatic events rointestinal and central nervous system events were the most common adverse experiences and had to discontinue therapy however the remaining 89 / tolerated tocainide satisfactorily

ocaine is the antiarrhythmic agent of choice the acute intravenous treatment of ventricu arrhythmias especially those occurring ear after acute infarction However lidocaine is ensively metabolized by the liver in a first pass ct and therefore cannot be given orally Con uently it has been necessary to use other iarrhythmics for continuous oral therapy ent efforts directed toward the development in oral antiarrhythmic of the same type as caine resulted in the synthesis of tocainide a lidocaine analogue that has a high bioavail ity when given orally and has an excellent ctrum of antiarrhythmic activity In this ly we report on the use of tocainide for the onic treatment of ventricular arrhythmias in a lticenter study involving many investigators arrhythmias were refractory to other thera and all patients had either failed to respond to were unable to tolerate other antiarrhythmic nts including quinidine procainamide diso amide and propranolol

terial and methods

total of 819 patients with severe refractory hythmias received the drug of whom 628 had an adequate trial of treatment and were docu mented sufficiently to allow an evaluation of the efficacy of tocainide therapy

Males outnumbered females by more than 2 1, and their ages ranged from 9 to 86 years with the *majority of patients being between 40 and 70* years old (Table I)

The most common etiology of the patients cardiac disease was atherosclerotic heart disease however a significant number of patients had cardiomyopathies or valvular heart disease (Ta ble II)

The patients had either ventricular tachycar dia or frequent and/or complex ventricular ectop ic beats The severity of their cardiac status was evaluated and 63% of them were categorized as New York Heart Association Class III or IV prior to tocainide therapy (Table III)

A further indication of the severity of the patients disease was the fact that 54% of them were receiving digitalis glycosides and 42 r required treatment with diuretics at some time during the study

Tocainide therapy was initiated on a 1 200 mg daily dose either as 400 mg t i d or 600 mg b i d which was then adjusted according to the patient s response The majority of patients received 1 200 to 2 400 mg daily in divided doses as shown in Table IV which shows the final regimen the patient received regardless of wheth

Astra Pharm ceutical Products In Framingham Mass
int req ests Mich el Young, M D Astra Pharm ceutical Prod I c P O Box 1089 Framingham MA 01701

-8/03/80/131041 + 05$00.50/0 © 1980 The C V Mosby Co

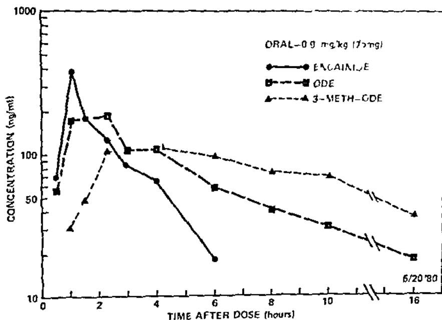


Fig. 7 Log of plasma concentration (*Cp*) of encainide and two of its major metabolites after oral administration in a patient with symptomatic PVCs (Courtesy Dr Robert Mayol Mead Johnson Pharmaceutical)

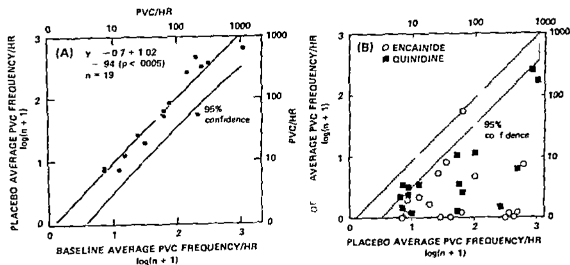


Fig. 8 Response of the log (n + 1) of PVCs in patients treated with encainide and quinidine on a plot of two prior determinations made by a linear regression analysis and the establishment of 95% confidence intervals (From Sami M Harrison DC Kraemer H Houston N Shimesaki B DeBusk RF The antiarrhythmic efficacy of encainide and quinidine Validation of a new model for drug assessment Am J Cardiol (In press.)

Comparison of encainide with quinidine The antiarrhythmic efficacy of encainide and quinidine was compared in 20 ambulatory men with a mean age of 56 years These patients had a history of chronic ischemic heart disease and were studied in a longitudinal crossover design with PVCs recorded on treadmill exercise tests and 24 hour ambulatory ECGs All patients had a baseline evaluation before entering the study and were then randomized to one of two drug sequences consisting of 2 weeks of placebo followed by 2 weeks of treatment with the first drug and a 1 week washout period after which the sequence was repeated with the second drug

In this comparison the reduction of average frequency of PVCs per hour on ambulatory ECGs

Table I Patients demographic data

Age (yr)	No	Male (%)	Female (%)
0-39	83	47	53
40 69	438	76	24
70 89	96	72	28
Unknown	11	45	55
Total	628	71	29

Table II Etiology of patients arrhythmias

Etiology	% of patients
Atherosclerotic heart disease	
Post AMI	61
Other	10
Cardiomyopathy	10
Mitral valve prolapse	5
Rheumatic heart disease	4
Unknown	10

AMI = acute myocardial infarction.

Table III New York Heart Association functional classification of cardiac status prior to treatment

Class	No
I	53
II	139
III	209
IV	122
Unknown	105

er a lower dose had been adequate for some time previously

The treatment is still ongoing At the time of this review of the program the majority of the patients had been treated for over 6 months and some for more than 3 years (Table V)

Results

Efficacy was assessed by the individual physician responsible for the patient The parameters used were clinical response and laboratory testing including Holter monitoring telemetry rhythm strips exercise testing controlled weaning after successful therapy and in a few cases programmed electrical stimulation studies

In addition we have arbitrarily decided that no patients would be considered to have been successfully treated if therapy was not given continuously for at least 1 month Therefore this is an

Table IV Final treatment regimen

Total daily dose (mg)	Daily regimen (mg)	No of patients	% of patients (n = 628)
1,200	400 q8h	109	17
1 200	600 q12h	30	5
1 600	400 q6h	37	6
1,800	600 q8h	147	23
2 400	600 q6h	30	5
2 400	800 q8h	73	12

evaluation of the efficacy of chronic oral therapy with tocainide

Overall 61% of the patients responded successfully to tocainide (Table VI) Of the 628 patients 252 (40%) had documented severe symptomatic arrhythmias and their symptomatic response to treatment was dramatic A total of 178 patients (71%) with symptomatic ventricular arrhythmias responded to tocainide and the majority of such responders (87%) showed total abolition of symptomatic arrhythmic events as shown in Table VII

Also a detailed evaluation of the symptomatic patients showed there was a greater than 90% reduction in emergency hospital admissions DC cardioversions syncope or presyncope during treatment with tocainide (Table VIII)

Tocainide had no clinically significant negative inotropic effect and was not noted to prolong Q T or QRS intervals during this chronic therapy study We obtained ECG data from patients on chronic therapy in excess of 6 months (Table IX) The early during treatment values were obtained from the first tracing taken after a steady state level of tocainide had been reached and the late during treatment values were obtained from the last tracing available for each patient but in no case were these values obtained less than 6 months into therapy The statistically significant reduction in Q T interval was not considered to be clinically significant

Side effects were generally either gastrointestinal or neurologic and of the 628 patients only 71 (11 3%) had to discontinue therapy because of an adverse experience as shown in Table X

Discussion

Over a period of almost two decades lidocaine has become established as the most effective agent for the suppression of ventricular arrhyth

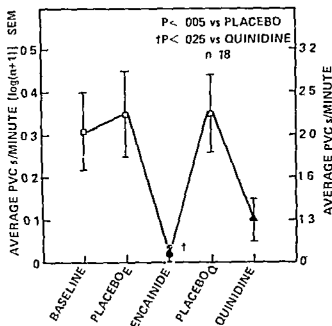


Fig 9 Mean and SEM for average frequency of PVCs in 20 patients determined by ambulatory monitoring while patients were receiving no drug (baseline) placebo before encainide and placebo$_Q$ before quinidine Average log (n + 1) and average PVCs per minute are shown (From Sami M Harrison DC Kraemer H Houston N Shinesaki B DeBusk RF The antiarrhythmic efficacy of encainide and quinidine Validation of a new model for drug assessment Am J Cardiol (In press)

was greater with encainide than with quinidine ($P > 0\ 01$) Similarly reductions in average frequencies of PVCs per minutes on treadmill testing were greater with encainide than with quinidine ($P > 0\ 025$) Encainide suppressed all PVCs in 44% of the patients and reduced them by at least 80% in 88% of the patients Encainide suppressed complex PVCs in 100% of the patients during 24 hours of ambulatory ECG recording In contrast none of the patients demonstrated total PVC depression with quinidine and only 44% demonstrated at least 80% reduction in PVC frequency with only 53% of the patients showing suppression of all complex PVCs during the 24 hour period of ambulatory ECG recording

The responses to quinidine and encainide were compared by means of a new statistical technique for antiarrhythmic drug efficacy based upon a linear regression analysis with determination of 95% and 99% confidence intervals when the variability for baseline and placebo measurements was compared Analysis was performed on a log (PVC frequency + 1) (Fig 8) When absolute responses to quinidine and encainide were compared with placebo the results showed a distinct advantage for encainide (Fig 9)

A systematic evaluation of side effects of the drug was performed in this study Comparison of side effects on placebo and during encainide and quinidine therapy are illustrated in Table III On placebo mild lightheadedness or dizziness and mild gastrointestinal effects were frequently noted With encainide therapy lightheadedness and dizziness of mild to moderate severity were noted in 11 of the patients This did not require discontinuation of the drug in any patients although the drug dose was lowered in four patients With quinidine gastrointestinal side effects were common occurring in 6 of 20 patients requiring reduction of the drug in three Fever was present in five patients treated with quinidine and a rash occurred in three while they were receiving quinidine (Table III)

Antiarrhythmic efficacy of encainide in patients with refractory recurrent arrhythmias New antiarrhythmic drugs are frequently studied in patients with refractory arrhythmias or in patients who cannot tolerate antiarrhythmic drugs currently available We have used encainide in 38 patients with recurrent ventricular tachycardia meeting these entry criteria In this group of patients the usual dose of encainide required ranged from 150 to 250 mg/24 hr Encainide completely eliminated recurrent ventricular tachycardia in 54% of the patients through 6 months of therapy and 29% of the patients between 18 and 30 months of therapy Twelve patients (32%) had side effects possibly due to encainide In four patients a ventricular arrhythmia of longer duration or more resistant to other forms of therapy occurred while the patient was receiving encainide In these patients it is reasonable to conclude that encainide may have worsened the arrhythmia

In our studies QRS prolongation appeared to correlate with antiarrhythmic effects in these patients with difficult and recurrent arrhythmias However these studies suggest that encainide is a safe and well tolerated antiarrhythmic drug in preventing recurrent ventricular tachycardia

Discussion

Preliminary studies with encainide suggest that this agent has important antiarrhythmic effects that permit its classification into a subcategory of Class 1 agents now available Our studies to date

Table V Duration of treatment with tocainide

Duration of treatment	*No of patients*
Greater than 3 yr	16 (3%)
From 2 to 3 yr	46 (7%)
From 1 to 2 yr	88 (14%)
6 mo to 1 yr	110 (18%)
From 1 to 6 mo	156 (25%)
Less than 1 mo	212 (34%)

mias[1,6] Unfortunately lidocaine cannot be used effectively by oral administration Tocainide is a lidocaine like agent that is active orally It has been reported to be effective in the treatment of ventricular arrhythmias in patients with coronary valvular and myopathic disease[7]

This study evaluated the responses to tocainide therapy of patients with severe refractory ventricular arrhythmias and the program was initiated as a humanitarian effort to treat these particularly difficult cases The severity of the patients condition was documented by the fact that 63% were New York Heart Association Class III or IV when tocainide therapy commenced and also by the fact that all the patients had failed to respond adequately to or could not take full dosages of other oral antiarrhythmic agents including quinidine procainamide propranolol and when available disopyramide In fact many patients could not be controlled adequately even on combinations of these agents

The etiologies of the patients cardiovascular diseases are shown in Table II and clearly indicate that although the majority of patients had atherosclerotic heart disease a considerable number had valvular and myopathic disease

Much has been written about the difficulty inherent in evaluating the response to antiarrhythmic therapy because of the variability in the frequency of ventricular ectopic beats in long term ECG monitoring[1,4] Despite this long term ECG monitoring is the basic parameter used to monitor the response to an antiarrhythmic agent Over 570 physicians were involved in this multicenter study of 628 patients and they evaluated the response to tocainide therapy by means of telemetry ECG rhythm strips 24 hour Holter recordings exercise testing and in a few cases programmed electrical stimulation also noted was the presence or absence of symptoms of ventricular arrhythmias In addition since these patients required maintenance therapy for con-

Table VI Response to treatment with tocainide

Therapeutic response	*No of patients*
Success	383 (61%)
Failure	245 (39%)

Table VII Degree of response of severe symptomatic arrhythmias to tocainide therapy

Duration of treatment	*Total abolition*	*Substantial reduction*	*No response*
Over 3 yr	12	–	–
2 to 3 yr	22	3	–
1 to 2 yr	23	10	–
6 mo to 1 yr	36	6	2
1 to 6 mo	61	5	18
Less than 1 mo	–	–	54
Total	154 (61%)	24 (10%)	74 (29%)

siderable periods this study evaluated treatment in excess of 1 month s duration That is to say although patients might be judged to have failed to respond to tocainide after an initial trial of as little as 3 days no patients were evaluated as showing a successful response to tocainide unless they had had at least 1 month s therapy In fact the majority of patients had been treated for over 6 months with tocainide

Overall 61% of the patients responded successfully to tocainide (Table VI) despite the refractory nature of the arrhythmias being treated and the most usual dosage was 600 mg t i d

Of the 628 patients it was particularly interesting to consider the symptomatic response to treatment of the 252 who had documented severely symptomatic arrhythmias Severe symptoms were defined as repeated occurrence of hospitalization ventricular tachycardia–ventricular fibrillation DC cardioversion syncope or multiple presyncopal episodes A total of 178 patients (71%) with these severe symptomatic ventricular arrhythmias responded to tocainide and of them the majority (87%) showed a total abolition of all symptomatic arrhythmic events (Table VII) Also a detailed evaluation of the symptomatic patients showed there was a greater than 90% reduction in emergency hospital admissions DC cardioversions syncope or presyncope during treatment with tocainide (Table VIII) This represents a considerable improvement in

Table III Side effects of encaindine quinidine and placebo

Side effects	Placebo (n = 20)		Encainide (n = [illegible]0)		Quinidine (n = [illegible])	
	Mild	Moderate/ severe	Mild	Moderate/ severe	Mild	Moderate/ severe
Lightheadedness or dizziness	4	2	[illegible]	4	5	
Gastrointestinal (nausea vomiting diarrhea)	8	1	2		6	
Fever	3	1	0	0	2	3
Rash	1	1	2	0	2	1

n = Number of patients.
Dose lowered to [illegible]5 mg in four patients
†Dose lowered to [illegible]00 mg in three patients.

suggest that this agent has important antiarrhythmic effects when administered to patients with frequent and complex ventricular arrhythmias[6-11]

Electrophysiologic studies in animals and humans demonstrate prolongation of His Purkinje conduction as evidenced by widening of the QRS complex and prolongation of the H V intervals [7] Little or no effects were noted on the sinus node atrial refractoriness A V node refractoriness or ventricular refractoriness Elevations of ventricular fibrillation threshold in animal studies suggest that this agent may be useful in preventing sudden death

In patients with normal ventricular function or only mildly altered ventricular function encainide produces little or no hemodynamic effects In patients with markedly depressed ventricular function elevated left ventricular end diastolic pressures and lowered cardiac output encainide reduces cardiac output slightly without altering the contractility indices or left ventricular end diastolic pressure These small changes in hemodynamics are in marked contrast to those recently reported for disopyramide

Antiarrhythmic efficacy In patients with ventricular premature beats both the oral and intravenous administration of encainide proved to be highly effective in reducing the frequency and complexity of ventricular premature beats In those patients with recurrent and resistant ventricular tachycardia encainide proved effective in more than half of such patients even when all other antiarrhythmic drugs had failed The maintenance of these patients for 18 to 30 months on encainide without recurrence of ventricular tachycardia seems important

In comparative studies with quinidine encainide was shown to be more effective in reducing ventricular premature beats and complex ventricular arrhythmias on ambulatory arrhythmia monitoring and treadmill testing Side effects for the drugs were of equal frequency in this cross over study design The side effects of encainide were those of central nervous system origin and those of quinidine of gastrointestinal origin or fever or rash A greater reduction in ventricular premature beats and complex forms was noted with encainide than with quinidine

Conclusions

Encainide is an important new antiarrhythmic drug It has proved to be highly effective in reducing ventricular premature beats and recurrent ventricular tachycardia There are few hemodynamic side effects The agent produces marked increase in His Purkinje conduction and a widening of the QRS complex which appears to occur on a dose related and plasma concentration basis Side effects of the drug are not severe although in a few patients the drug appears to enhance the occurrence and severity of reentry cardiac arrhythmias

REFERENCES

1. Harrison DC Meffin PJ Winkle RA Clinical pharmacokinetics of antiarrhythmic drugs Prog Cardiovasc Dis 20 21[illegible] 1977
2. Zipes DP Troup PJ New antiarrhythmic agents. Amiodarone aprindine disopyramide ethmozin mexiletine tocainide verapamil Am J Cardiol 41 1005 19[illegible]8
3. Byrne JE Gomoll AW Antiarrhythmic activity of MJ 9067 Fed Proc 32 81[illegible] 1973 (Abst)
4. Byrne JE Gomoll AW McKinney GR Antiarrhythmic properties of MJ 9067 in acute animal models J Pharmacol Exp Ther 200 14[illegible] 19[illegible]
5. Gibson JK, Somani P Bassett AL Electrophysiologic

Table VIII Symptomatic events in 252 severely symptomatic patients

Arrhythmic events	No of patients	No of occurrences: Before treatment	During treatment	% Reduction
Emergency admission for VT/VF	129	364	26	93
DC cardioversion for VT/VF	112	512	17	97
Episodes of syncope	104	403	11	97
Episodes of presyncope	57	756	6	99

Table IX ECG intervals before and during long term tocainide therapy in 22 patients

Evaluation period	P R interval (mean ± SD)	QRS interval (mean ± SD)	QT interval (mean ± SD)
Pretreatment	0.173 ± 0.021	0.093 ± 0.030	0.450 ± 0.044
Early during treatment	0.0171 ± 0.021	0.093 ± 0.030	0.431 ± 0.046
Late during treatment	0.175 ± 0.025	0.095 ± 0.029	0.436 ± 0.055

$0.05 > P > 0.01$

Table X Adverse experiences resulting in discontinuation of tocainide in 628 patients who were valid for evaluation of efficacy

Reason for discontinuation	% of patients
CNS	4.9
GI	2.4
CNS/GI	1.6
Rash	2.1
Increased CHF	0.3
Total	11.3

Abbreviations CNS = central nervous system GI = gastrointestinal CHF = congestive heart failure

the morbidity rate for these severely symptomatic patients

Tocainide had no clinically significant negative inotropic effect in hemodynamic studies and was not noted to prolong Q T or QRS intervals in electrophysiologic studies During this chronic therapy study we obtained ECG data from patients on therapy in excess of 6 months The early during treatment values (Table IX) were obtained from the first tracing taken after a steady state level of tocainide had been reached and the late during treatment values were obtained from the last tracing available for each patient but in no case was the value obtained less than 6 months into therapy There was no significant prolongation of either Q T or QRS intervals A statistically significant reduction in Q T interval was seen however this was not considered to be clinically significant

The side effects to tocainide are generally those to be expected for a lidocaine analogue and have been discussed in detail elsewhere[1] In this study only 11% of the 628 patients treated with tocainide had to discontinue therapy because of side effects and the remaining 89% tolerated the tocainide therapy satisfactorily

We conclude that tocainide is an effective and safe agent for the management of refractory ventricular arrhythmias

REFERENCES

1 Modell W Drugs of choice 1980 1981 St Louis 1980 The CV Mosby Company pp 398 399
2 American Medical Association drug evaluations, ed 4 New York 1980 John Wiley & Sons Inc p 515
3 The Medical Letter Series vol 20 New York 1978 The Medical Letter Inc pp 116 117
4 Harrison DC Sprouse JH Morrow AG Antiarrhythmic properties of lidocaine and procainamide Clinical and physiologic studies of their cardiovascular effects in man Circulation 23 486-91 1963
5 Gianelly R Van der Groeben JO Spivack AP Harrison DC Effect of lidocaine on ventricular arrhythmias in patients with coronary heart disease N Engl J Med 277 1215-21 1967
6 Lown B Kosowsky BD Klein MD Pathogenesis, prevention and treatment of arrhythmias in myocardial infarction Circulation 40 261 65 1968
7 Coltart DJ Berndt TB Harrison DC Antiarrhythmic and circulatory effects of Astra W36095 A new lidocaine-like agent Am J Cardiol 34 35-41 1974
8 Moore EN Spear JF Horrowitz LN Feldman HS Mollar RA Electrophysiologic properties of the new antiarrhythmic drug tocainide Am J Cardiol 41 703 9 1978
9 Woosley RL McDevitt DG Nies AS Smith RF Williamson AR Oates JR Suppression of ventricular ectopic depolarizations by tocainide Circulation 56 980 4 1977
10 Winkle RA Meffin PJ Fitzgerald JW Harrison DC Clinical efficacy and pharmacokinetics of a new orally effective antiarrhythmic tocainide Circulation 54 884 9 1971

effects of encainide (MJ 9067) on canine Purkinje fibres Eur J Pharmacol 52 161 1978
6 Sami M Mason JW Oh G Harrison DC Canine electrophysiology of encainide a new antiarrhythmic drug Am J Cardiol 43 1149 1979
7 Sami M Mason JW Peters F Harrison DC Electrophysiologic effects of encainide a newly developed antiarrhythmic Am J Cardiol 44 526 1979
8 Jaillon P De La Rosa S Griffin JC Winkle RA Harrison DC Effects of encainide (MJ 9067) on the ventricular fibrillation threshold in anesthetized dogs J Cardiovasc Pharmacol 2 517 1980
9 Mason JW Peters FA Successful treatment of life threatening ventricular arrhythmias with encainide Clin Res 27 566A 1979 (Abst)
10 Winkle RA Peters F Kates RE Tucker C Harrison DC The clinical pharmacology and antiarrhythmic efficacy of encainide in patients with chronic ventricular arrhythmias Circulation (Submitted for publication)
11 Sami M Harrison DC Kraemer H Houston N Shimesaki B DeBusk RF The antiarrhythmic efficacy of encainide and quinidine Validation of a new model for drug assessment Am J Cardiol (In press.)
12 Tucker C Winkle RA Peters F Kates RE Harrison DC The acute hemodynamic effects of intravenous encainide in patients with heart disease Circulation. (Submitted for publication)
13. Sami M Kraemer H Harrison DC Houston Miller N Shimesaki B DeBusk RF A new method for evaluating antiarrhythmic drug efficacy in individual patients. Circulation (In press)

11 Morganroth J Michelson EL Horrowitz LN Josephson ME Pearlman AS Dunkman WB Limitations of routine long term electrocardiographic monitoring to assess ventricular ectopic frequency Circulation 58 408 14 1978
12 Winkle RA Meffin PJ Harrison DC Long term tocainide therapy for ventricular arrhythmias Circulation 57 1008 16 1978
13 Kraemer HC Principles and problems of controlled study design Proceedings of Symposium on Cardiac Arrhythmias A Decade of Progress—1980 Boston G K Hall & Co (In press)
14 Horn HR Hadidian Z Johnson JL Vassallo HG Williams JH Young MD Safety evaluation of tocainide in the American Emergency Use Program Am HEART J 100 1037-40 1980

Studies with aprindine

Douglas P Zipes MD Victor Elharrar PhD Robert F Gilmour Jr PhD James J Heger MD and Eric N Prystowsky MD
Indianapolis Ind

Aprindine is a very effective antiarrhythmic agent with a narrow therapeutic toxic ratio It has been used successfully in treating patients who have both supraventricular and ventricular tachyarrhythmias Aprindine slows conduction in all cardiac fibers and suppresses digitalis induced after-depolarizations Voltage-clamp studies indicate that aprindine in higher doses suppresses the slow inward current in frog atria In the dog subjected to coronary artery occlusion aprindine may be arrhythmogenic antiarrhythmic or have no effect on the development of arrhythmias depending on the temporal relationship between time of administration and time of occlusion

Aprindine an antiarrhythmic agent with prominent local anesthetic effects was developed and used initially in Belgium It is available clinically throughout most of Europe and is being evaluated as an investigational agent at a number of centers in the United States

Clinical experience

Early studies[1] established aprindine as an effective antiarrhythmic agent against a variety of supraventricular and ventricular arrhythmias that occurred in patients with different types of heart disease

In our initial experience with aprindine we treated 23 patients with recurrent ventricular tachycardia (10 patients) or recurrent ventricular tachycardia and ventricular fibrillation In the group with only ventricular tachycardia aprindine prevented further episodes in eight patients failed to prevent ventricular tachycardia in one patient and converted sustained episodes of ventricular tachycardia to short asymptomatic bursts in one patient In the group with ventricular tachycardia and ventricular fibrillation aprindine prevented further recurrences in all but one patient who continued to have recurrent episodes of ventricular tachycardia One responder had to stop taking the drug because of intolerable side effects Thus among the 23 patients aprindine was not tolerated by one patient and failed to control the ventricular arrhythmia in two patients In five responders aprindine plus propranolol (one patient) aprindine plus quinidine (three patients) and aprindine plus permanent ventricular pacing (one patient) achieved better suppression than aprindine alone Subsequent to this first study we successfully treated seven patients who had ventricular tachycardia associated with mitral valve prolapse[3]

Aprindine has also been used to treat patients with supraventricular arrhythmias Recently we reported our experience with the use of aprindine in treating 10 patients with recurrent or continuous supraventricular tachycardia that was difficult to control with conventional arrhythmic agents Nine patients had Wolff Parkinson White syndrome During administration of aprindine circus movement supraventricular tachycardia could no longer be initiated in four patients and was initiated with difficulty in two patients and with greater ease in two patients In one patient aprindine therapy slowed the ventricular response during atrial

From the Krannert Institute of Cardiology the Department of Medicine Indiana University School of Medicine and the Veterans Administration Hospital Indianapolis Ind

Supported in part by the Herman C Krannert Fund, by grants HL-06308 HL-0 18 and HL-18795 from the National Heart Lung and Blood Institute National Institutes of Health and by the American Heart Association, Indiana Affiliate Inc

Reprint requests Douglas P Zipes MD Indiana University School of Medicine 1100 W Michigan St Indianapolis, IN 46223

0002 8703/80/131065 + 08$00.80/0 © 1980 The C V Mosby Co

IV Antiarrhythmic studies with newer agents

Encainide A new and potent antiarrhythmic agent

Donald C Harrison M D Roger Winkle M D Magdi Sami M D and Jay Mason M D *Stanford Calif and Montreal Canada*

Encainide is a potent Class I antiarrhythmic drug that prolongs conduction in the His Purkinje system It produces only minimal hemodynamic changes in the normal or depressed left ventricle Studies to date demonstrate excellent effectiveness against ventricular arrhythmia and in comparative stud es with quinidine encainide was superior in reducing the frequency and complexity of ventricular premature beats in patients late after myocardial infarction

Although a number of new antiarrhythmic agents have been introduced for clinical trials in the United States during the past decade there continues to be a need to find more potent and safer new antiarrhythmic agents[1] No available agent has proved to be entirely satisfactory in preventing sudden arrhythmic deaths in coronary artery disease and cardiomyopathies On the other hand several new agents have been documented to be effective in reducing the frequency of less serious ventricular arrhythmias in patients in whom they are tried

Another shortcoming of available antiarrhythmic agents is their limiting pharmacokinetic properties They are not ideal in that they must be administered on a schedule of frequent dosing and several of them are metabolized or excreted rapidly thereby lacking a prolonged duration of action

Encainide which has a new molecular structure was recently introduced for clinical trial as an antiarrhythmic agent Its cellular effect is to decrease phase zero of the action potential (dV/dt) thereby placing it among Class I antiarrhythmic drugs It produces little change in the duration of the action potential when studied in isolated cells suggesting that it would have little effect on repolarization in the intact heart

From the Division [illegible] Medicine Stanford [illegible] Montreal Canada

Reprint request Donald C Harrison M [illegible] Stanford University School of Med [illegible]

Methods and results

During the past 3 years we have performed extensive studies with encainide to elucidate its electrophysiologic effects, its pharmacokinetics its antiarrhythmic spectrum of activity and its safety when administered to patients with heart disease The scope of our studies is outlined in Table I

Electrophysiologic studies in animals After cellular studies demonstrated that encainide has the potential for being an antiarrhythmic drug with high potency it was evaluated in a series of animal studies to detect its effect on cardiac conduction Mongrel dogs anesthetized with chloralose were divided into four groups Group 1 was a control group Groups 2 3 and 4 were groups to be administered encainide in a dose of 0 3 0 9 and 2 7 mg/kg body weight respectively during an intravenous infusion of 15 minutes duration Plasma concentrations of drug blood pressure electrocardiograms and atrial and His bundle electrograms were recorded before durin and after administration of the drug for a total o 120 minutes Heart rate A H and H V intervals the QRS complex and QT intervals were measured every 5 minutes during sinus rhythm and with a constant heart rate provided by atria pacing In addition sinus node recovery times and atrial and atrioventricular (A V) nodal and lef ventricular refractory periods were measured before and immediately after infusion and every 30 minutes for 2 hours

The plasma concentrations of the drug tha were achieved in these animals are illustrated i

0002-8703/80/131046 + 09$00 90/0 © 1980 The C V Mosby C

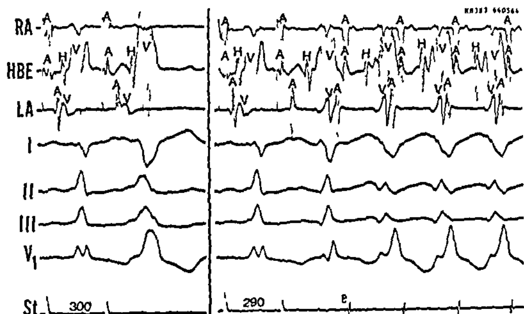


Fig 1A Control recording before treatment with aprindine Determination of antegrade effective refractory period of accessory pathway and initiation of paroxysmal supraventricular tachycardia in a patient with type A Wolff Parkinson White syndrome After the last driven impulse of the basic train premature stimulation of right atrium at a coupling interval of 300 msec resulted in antegrade conduction over the accessory pathway Activation of bundle of His occurred after onset of QRS complex Premature right atrial stimulation at a coupling interval of 290 msec blocked in antegrade fashion in accessory pathway conducted to ventricle with a right bundle branch block and initiated paroxysmal supraventricular tachycardia during which activation of left atrium preceded activation of low and high right atrial sites These findings are consistent with presence of left sided bypass tract From top to bottom right atrial electrogram (*RA*) His bundle electrogram (*HBE*) left atrial electrogram (LA) scalar leads I II III and V and stimulus channel (*St*) Paper speed is 100 mm/sec numbers indicate milliseconds *A* = atrial potential *e* = electrogram recorded at the site of stimulation *H* = His bundle potential V = ventricular potential Of the paced beats only the last in the basic train and the premature stimulus are displayed (From Zipes DP Gaum WE Foster PR Rosen KM Delon W Amat Y Leon F Noble RJ Aprindine treatment of supraventricular tachycardias With particular application to Wolff Parkinson White syndrome Am J Cardiol 40 586 1977)

flutter from 1 1 conduction over the accessory pathway to 2 1 conduction over the normal pathway in another patient it slowed the ventricular rate during atrial fibrillation from 140 to 180 to 80 to 100 beats/min Thus eight patients had an excellent clinical response but treatment with aprindine was discontinued in two patients Electrophysiologic evaluation revealed that aprindine produced complete block or increased refractoriness of the accessory pathway in an anterograde direction in all patients and in a retrograde direction in all but two patients tested (Fig 1)

Our total current experience includes 152 patients treated with aprindine for a variety of tachyarrhythmias including 130 patients with ventricular tachycardia (Fig 2) 15 patients with supraventricular tachycardia four patients with premature ventricular complexes (PVCs) two patients with atrial fibrillation and one patient with atrial tachycardia Fifty seven patients continue to receive aprindine (range 1 to 40 months) for ventricular arrhythmias (53 patients) and supraventricular arrhythmia (four patients) Reasons for discontinuing the drug include inadequate control of ventricular arrhythmias (50 patients) of supraventricular arrhythmias (nine patients) or exacerbation of ventricular arrhythmias (five patients) In two patients the arrhythmia resolved and the drug was stopped in two patients for noncompliance Fourteen patients discontinued aprindine because of side effects and 13 patients died while receiving the drug although in none was the drug implicated as a cause of death

Side effects

The toxic therapeutic ratio for aprindine is rather narrow and side effects particularly during the initial loading period and adjustment of the maintenance dose are common These side

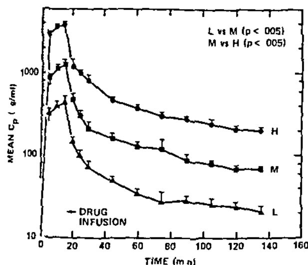
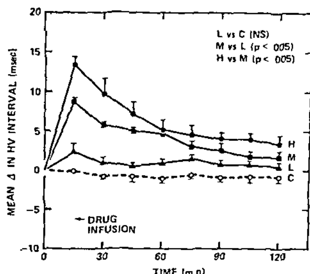


Fig 1 Plasma concentration (*Cp*) of encainide with time for high dose (*H*) of 2 7 mg/kg in seven dogs medium dose (*M*) of 0 9 mg/kg in four dogs and low dose (*L*) of 0 3 mg/kg in four dogs The shaded area indicates the 15 minute period of drug infusion Statistical intergroup differences were evaluated at the end of the infusion period (From Sami M Mason JW Harrison DC Canine electrophysiology of encainide a new antiarrhythmic Am J Cardiol 43 1149 1979)

Fig 1 Peak plasma concentrations averaged 415 ng/ml in Group 2 1 300 ng/ml in Group 3 and 4 000 ng/ml in Group 4 The disappearance from plasma was fitted to a two compartment pharmacologic model with linear kinetics

Blood pressure was not altered at any dosage level throughout the study Heart rate was insignificantly changed The duration of the QRS complex was prolonged and could be related to the plasma concentration of the drug (Fig 2) H V intervals were prolonged at all doses (Fig 2) The effects on H V interval and QRS duration in relation to plasma concentration could be linearized when log plasma concentration was plotted against the change in electrophysiology produced by the specific agent (Fig 3) There was no significant change in heart rate corrected sinus node recovery time A H intervals QT intervals or atrial A V nodal or left ventricular refractory periods We concluded that encainide was different from clinically available antiarrhythmic agents in that it prolonged His Purkinje system conduction without significantly affecting conduction or refractoriness of other parts of the cardiac conduction system in animals

With the completion of these studies and no documented specific adverse hemodynamic or electrophysiologic effects we proceeded to study



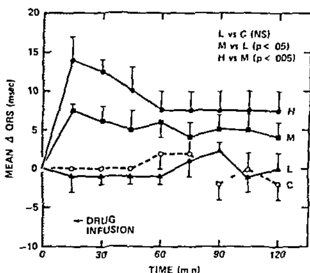


Fig 2 Temporal changes (Δ) in the mean H V interval (*top*) and QRS duration (*bottom*) in five control animals (*C*) and four animals receiving a low (*L*) dose (0 3 mg/kg) four receiving a medium (*M*) dose (0 9 mg/kg) and seven receiving a high dose (*H*) (2 7 mg/kg) of encainide Statistical intergroup differences were evaluated at the end of the infusion period (T) *NS* = not significant *P* = probability (From Sami M Mason JW Harrison DC Canine electrophysiology of encainide a new antiarrhythmic Am J Cardiol 43 1149 1979)

the effects of encainide on ventricular fibrillation threshold which has been used as a measure of the effects of an antiarrhythmic drug in preventing ventricular fibrillation

We *demonstrated a stepwise progressive* increase in ventricular fibrillation threshold with progressively greater doses and plasma concentrations of encainide These studies were per

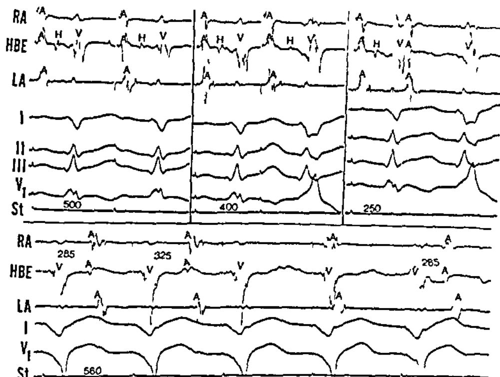


Fig 1B Complete antegrade and retrograde block in accessory pathway during administration of aprindine Top panels display the last driven beat of the basic train and the premature right atrial stimulus delivered at coupling intervals of 500 400 and 250 msec respectively Both basic and premature beats are conducted to ventricles over the normal pathway with a right bundle branch block similar to the contour of the QRS complex initiated during supraventricular tachycardia seen in Fig 1A His bundle activation was slurred and delayed after premature stimulation at intervals of 500 and 400 msec after premature stimulation at 250 msec a clear His bundle spike could not be recorded Supraventricular tachycardia could not be initiated at any coupling interval. Bottom panel shows right ventricle being stimulated at a constant cycle length of 560 msec Note that low right atrial activation preceded high right atrial activation and that the latter preceded left atrial activation This sequence of retrograde atrial activation is entirely different from the corresponding sequence that occurred during supraventricular tachycardia seen in Fig 1A Complete retrograde block in the accessory pathway is present Note also that a retrograde Wenckebach block occurred in the normal pathway the VA interval progressively lengthened culminating in VA block after the third QRS complex The third P wave is probably a sinus initiated P wave Conventions same as in Fig 1A Same patient as in Fig 1A (From Zipes DP Gaum WE Foster PR Rosen KM Delon W Amat Y Leon F Noble RJ Aprindine treatment of supraventricular tachycardias With particular application to Wolff Parkinson White syndrome Am J Cardiol 40 586 1977)

effects related to the dose and serum concentration of aprindine include most commonly a tremor of the hand and fingers As the serum concentration increases dizziness intention tremor ataxia nervousness hallucinations diplopia memory impairment or seizures may also occur Neurologic side effects are minimal or absent at serum aprindine concentrations of less then 1 µg/ml Gastrointestinal side effects are more infrequent than neurologic side effects

Recently cholestatic jaundice and agranulocytosis[7] have been reported to occur in association with the use of aprindine and are thought to be idiosyncratic reactions as opposed to dose related toxicity The problems have generally occurred between the fourth and sixteenth weeks of aprindine therapy and with an estimated incidence of approximately one in several thousand based on data from Europe In the United States of approximately 1 500 patients treated 10 have developed agranulocytosis (WBC <500 ml) Eight patients recovered after aprindine was discontinued One of these patients died of ventricular fibrillation 24 hours after discontinuation of aprindine In addition about one in every 30 patients has exhibited a WBC <1 500 ml The majority of these patients had normal WBC counts subsequently in spite of continuing aprindine Only one patient had aprindine discontinued because of a WBC <1 500 ml[3] It is possible

Table I Stanford studies with encainide

Animal studies	*Human studies*
Basic electrophysiology in canine model	Basic electrophysiology with normal cardiac conduction
Encainide's effects on ventricular fibrillation threshold	Hemodynamic actions of encainide in normal and depressed ventricle
Action of encainide on monophasic action potential by endocardial electrode techniques	Single dose efficacy and pharmacokinetics in symptomatic ventricular arrhythmias
	Encainide in life threatening ventricular tachycardia
	Comparison of quinidine and encainide on arrhythmias late after infarction
	Safety and long term efficacy of encainide

formed in an animal model in which lidocaine was demonstrated to increase the ventricular fibrillation threshold as a prototypical response Specific examples of the increase in ventricular fibrillation thresholds as compared to control are illustrated in Fig 4

Additional studies in animal models utilizing endocardial electrosuction techniques for studying simulated action potentials from intact animal preparation were utilized for studying the cardiac effects of encainide Dose and plasma concentration related effects on the slope of phase zero (dV/dt) of these endocardial action potentials were demonstrated together with moderate prolongation of the duration of the action potential Detailed results of these studies are to be published

Clinical electrophysiologic effects of encainide Following the demonstration that encainide had important electrophysiologic properties in animals studies were carried out in patients undergoing electrophysiologic studies in the cardiac catheterization laboratory [9] Standard His electrograms were recorded in 10 patients with coronary artery disease before and after the administration of encainide Five patients were given 0 6 mg/kg and five patients 0 9 mg/kg intravenously during a constant infusion of 15 minutes duration Plasma concentrations of encainide heart rate blood pressure and conduction intervals were measured before during and after encainide infusion In addition sinus node recovery time Wenckebach cycle length and atrial A V nodal and right ventricular refractory periods were measured before and after the encainide infusion The average peak plasma concentration was 0 49 ± 0 35 μg ml (mean ± standard error of the mean) in the 10 patients studied

Encainide significantly prolonged H V and QRS intervals in all patients by an average of 31 ± 7% and 18 ± 9% SD ($P < 0\ 001$) respectively (Fig 5) An increase in the Q T interval was also observed after encainide infusion (2% ± 9%) but no significant changes were noted in heart rate blood pressure A H intervals corrected sinus node recovery time, Wenckebach cycle length refractory periods of the atrium A V node or right ventricle From these studies we concluded that encainide significantly prolonged conduction in the His Purkinje system without markedly affecting conduction or refractoriness of other parts of the cardiac conduction system in man No consistent hemodynamic effect was observed in the 10 patients included in this study Significant correlation of the plasma concentration with the electrophysiologic effects was observed [9]

Single dose efficacy and pharmacokinetics In order to evaluate the pharmacokinetic and single dose efficacy of encainide nine hospitalized patients with frequent and complex ventricular premature beats were studied in a 3 day double blind protocol Each day patients received either encainide 75 mg intravenously encainide 75 mg orally or an appropriate placebo Frequent plasma samples for encainide concentration were taken and continuous ambulatory electrocardiograms recorded [1]

Eight of the nine patients were documented to have antiarrhythmic effects due to encainide (Fig 6) The inclusion of a placebo day provides a control against attributing spontaneous variation of premature ventricular contraction (PVC) frequency to encainide's antiarrhythmic effects The duration of continuous 90% or greater suppression of PVCs after intravenous encainide ranged from 5 to 36 hours The antiarrhythmic efficacy of

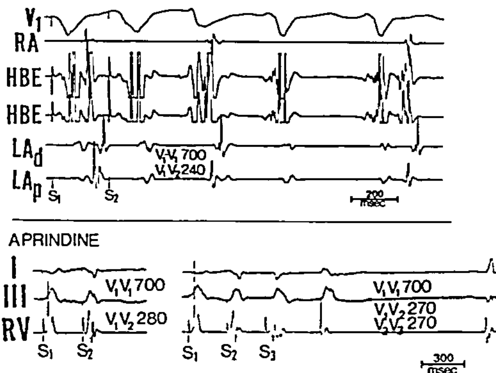


Fig 2 Initiation of ventricular tachycardia (*top panel*) during premature right ventricular stimulation at interval of 240 msec. After aprindine administration (*bottom panel*) only a single spontaneous ventricular extrasystole followed two premature ventricular stimuli. LA_d = left atrium near appendage LA_p = left atrium near septum, recorded with a catheter passed across a patient's foramen ovale

that all of these cases of leukopenia were not related to aprindine Transient abnormalities in liver function tests have been noted in some of our patients but no abnormality has persisted or has led to discontinuation of the drug

Clinical pharmacology

Aprindine is well absorbed has high systemic availability and is 85% to 95% protein bound Approximately 95% of the hydroxylated metabolites undergo glucuronidation in the liver Sixty five percent of aprindine and its metabolites is found in the urine with the remaining 35% in the feces Elimination half life has ranged from 13 to 50 hours (mean 27 9 hours) in one study 20 hours to 30 hours in another and 18 hours (mean) in a third.[19] The N-desethyl metabolite is present in small amounts in the plasma of patients treated chronically with aprindine and exerts some antiarrhythmic actions Clinically the full antiarrhythmic effect of aprindine may not occur for several days even when the drug is initially administered in a loading dose

Hemodynamic studies have revealed that therapeutic doses of aprindine mildly depressed myocardial function In man aprindine (200 mg orally) slightly decreased systolic and mean aortic blood pressure during exercise in one study[4] and slightly depressed myocardial contractility when given intravenously (100 mg) in another At a total dose of 140 or 150 mg intravenously aprindine produced a moderate and dose related decrease in peak left ventricular dP/dt and V_m [5]

Electrophysiology

In isolated cardiac preparations aprindine shortened the duration of the action potential and effective refractory period of Purkinje fibers the former was shortened more than the latter [7-9] However in cardiac muscle fibers action potential duration was only slightly reduced and the duration of the effective refractory period was lengthened. The rate of rise of phase 0 was depressed more so at rapid rates at higher potassium levels and to a greater degree than with comparable amounts of lidocaine [9] Diastolic depolarization and spontaneous firing were depressed or abolished by aprindine Aprindine also reduced digitalis induced increases in potas

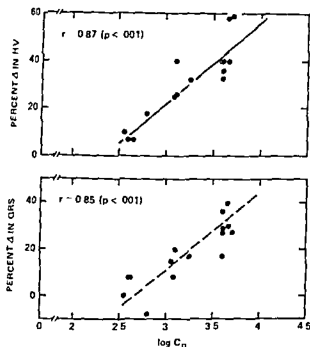


Fig 3 Linear regression of the change in (Δ) of the H V interval and the QRS duration and the log plasma concentration (*Cp*) of encainide at the end of a 15 minute infusion for all 15 animals in this study *P* = probability *r* = correlation coefficient (From Sami M Mason JW Harrison DC Canine electrophysiology of encainide a new antiarrhythmic Am J Cardiol 43 1149 19 9)

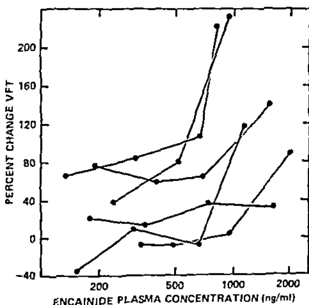


Fig 4 Percentage of increase in ventricular fibrillation threshold (*VFT*) in relation to plasma concentration for encainide for six dogs.

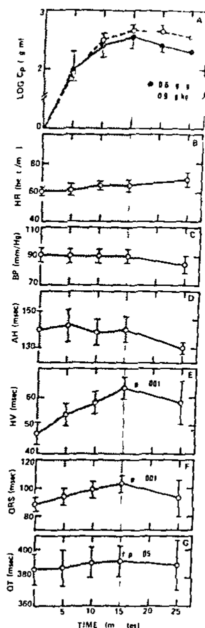
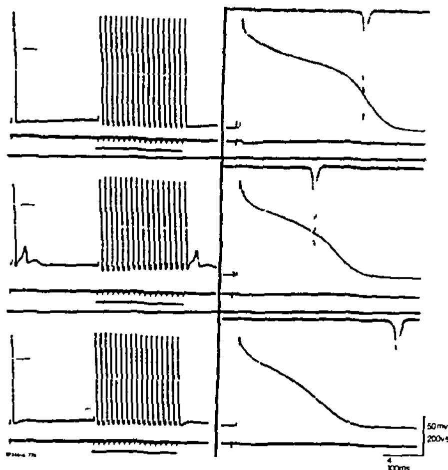


Fig 5 C mparati t mp ral changes in selected measurements made during i t t it base atri l pacing In panel *A* data for the five pati nt gi en 0 C mg/kg and the five patients given 0 9 mg/kg of en aini le are plotted separately In panels *B* through *G* the data are ombined for the two groups Mean values (open circles) + stan lard error of the mean (bars) are plotted at time 0 (control) during encainide infu ion (haded area) and after encaini le infu i n (15 to ? minutes) From top to bottom *Cp* = plasma concentration of encainide *HR* = heart rate *BP* = mean aortic l lood pressure *A H* interval *H V* interval *QRS* durati n *Q T* interval Significance levels were mea ured at end f infu ion (t = 15 minutes) *P* < 0 001 *P* < 0 01 Bars indicate stan lard (From Sami M Mason JW I cters F Harri on DC El ctrophysiologic effects of encainide a newly devel ped antiarrhythmic Am J Cardiol 44 6 19?9)



Fg 3 Effect of aprındıne (3 × 10 M) on tran ıent depolarızatıon ınduced by acetylstrophanthıdın (1 7 × 10 M) From top to bottom the traces of each panel ın the left hand column represent the transmembrane actıon potentıal the bıpolar electrogram and the stımulatıon perıod (8 sec) at a cycle length of 500 msec In the rıght hand column the traces represent (from top to bottom) the dV/dt of the upstroke the transmembrane actıon potentıal and the bıpolar electrogram *Upper panel* Control recordıng *Middle panel* After 32 mınutes of superfusıon wıth acetylstrophanthıdın (1 ı × 10 M) *Lower panel* Nıne mınutes after superfusıon wıth aprındıne (3 × 10 M) All recordıngs were obtaıned from the same ımpalement (From Elharrar V Baıley JC Lathrop DA Zıpes, DP Effects of aprındıne HCl on slow channel actıon potentıals and transıent depolarızatıon ın canıne Purkınje fıbers J Pharmacol Exp Ther 205 410 1978)

sıum permeabılıty [?] and suppressed transıent depolarızatıons caused by acetylstrophanthıdın ın canıne Purkınje fıbers (Fıg 3) [30] Aprındıne does not appear to affect slow channel actıvıty of canıne Purkınje fıbers at concentratıons of 3 × 10 [6] to 1 × 10 M (Fıg 4)

The effects of aprındıne on transmembrane currents ın frog (*Rana rıdıbunda*) atrıal trabeculae have been studıed by means of a voltage clamp technıque Aprındıne (1 × 10 gm/ml) reduced maxımum ınward sodıum current by 38 6 ± 7 2% (mean ± SEM n = 6) but had no effect on the slow ınward current or outward current A hıgher dose of aprındıne (2 8 × 10 gm/ml) suppressed both the fast ınward current and the slow ınward current Aprındıne (2 8 × 10 [5] gm/ml) also depressed slow channel dependent membrane oscıllatıons ınduced ın atrıal trabeculae by ınjectıon of current pulses These data ındıcate that aprındıne possesses fast and slow channel blockıng propertıes ın the frog the latter beıng more apparent at hıgh concentratıons of the drug

Studıes ın ıntact dogs have revealed that aprındıne ınjected ınto the sınus nodal artery decreased the spontaneous sınus rate and ınjected ınto the A V nodal artery prolonged the functıonal refractory perıod and conductıon tıme

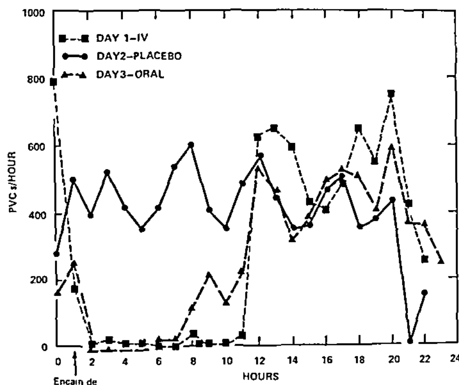


Fig 6 Premature ventricular contraction (PVC) frequency per hour response to placebo (●) oral encainide (▲) and intravenous encainide (■) in a patient with frequent and symptomatic PVCs.

Table II Encainide pharmacokinetics in nine subjects (mean ± SEM)

Pharmacokinetics	Results
Half life (hr)	
Intravenous	3 38 ± 0 56 (mean + SEM)
Oral	2 47 ± 0 76
Bioavailability (%)	41 9
Clearances (ml/min/kg)	13 2 ± 1 87
Antiarrhythmic offset plasma concentration (ng/ml)	
Intravenous	39 0 ± 19 3
Oral	14 76 ± 5 73

encainide in these studies following oral administration was equal to that of intravenous administration Following oral administration the duration of effect was greater in most patients than for the intravenous administration suggesting the presence of an active metabolite In several patients a new high pressure liquid chromatography (HPLC) assay was used to detect these metabolites (Fig 7) The kinetics and physiologic action of these metabolites are now under further study

Pharmacokinetic studies demonstrated a marked intersubject variation in bioavailability (mean 42 ± 24%) clearance (13 2 ml ± 5 6 ml/min/kg) and half life (3 4 ± 1 7 hours intravenously 2 5 ± 0 8 hours orally) (Table II) Minimal antiarrhythmic plasma concentration was higher (39 ± 54 ng/ml) after intravenous dosing than after oral dosing (14 ± 16 ng/ml) suggestin an active metabolite after oral dosing in many of the patients Minimal side effects were seen despite high peak plasma concentration (range 794 to 1 556 ng/ml intravenously 36 to 495 ng/ml orally) The minimal ratio of toxic to therapeutic plasma concentration ranged from 4 3 to 326 with a median value of 27 after oral dosing Antiarrhythmic action was associated with 11% to 44% widening of the QRS complex which did not correlate with any other adverse side effects seen From these studies we believe that encainide is a highly effective agent for suppressing ventricular arrhythmias In spite of a wide range of bioavailability high plasma clearance and relatively short half life its wide toxic to therapeutic ratio and the existence of an active metabolite permits a long duration of action that should allow a reasonable dosing schedule in most patients by the oral route [10]

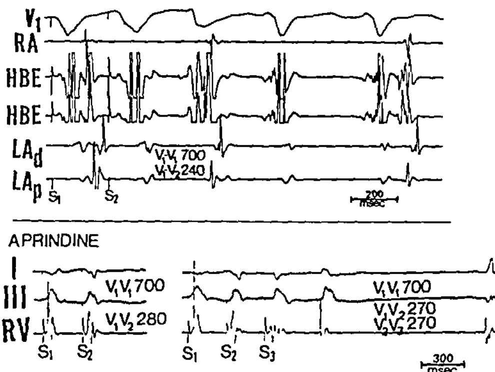


Fig 2 Initiation of ventricular tachycardia (*top panel*) during premature right ventricular stimulation at interval of 240 msec After aprindine administration (*bottom panel*) only a single spontaneous ventricular extrasystole followed two premature ventricular stimuli LA_d = left atrium near appendage LA_p = left atrium near septum recorded with a catheter passed across a patient s foramen ovale

that all of these cases of leukopenia were not related to aprindine Transient abnormalities in liver function tests have been noted in some of our patients but no abnormality has persisted or has led to discontinuation of the drug

Clinical pharmacology

Aprindine is well absorbed has high systemic availability and is 85% to 95% protein bound Approximately 95% of the hydroxylated metabolites undergo glucuronidation in the liver Sixty five percent of aprindine and its metabolites is found in the urine with the remaining 35% in the feces[4] Elimination half life has ranged from 13 to 50 hours (mean 27 9 hours) in one study[4] 20 hours to 30 hours in another[18] and 18 hours (mean) in a third[19] The *N* desethyl metabolite is present in small amounts in the plasma of patients treated chronically with aprindine and exerts some antiarrhythmic actions[1] Clinically the full antiarrhythmic effect of aprindine may not occur for several days even when the drug is initially administered in a loading dose

Hemodynamic studies have revealed that therapeutic doses of aprindine mildly depressed myocardial function [illegible] In man aprindine (200 mg orally) slightly decreased systolic and mean aortic blood pressure during exercise in one study and slightly depressed myocardial contractility when given intravenously (100 mg) in another At a total dose of 140 or 150 mg intravenously aprindine produced a moderate and dose related decrease in peak left ventricular dP/dt and V_m

Electrophysiology

In isolated cardiac preparations aprindine shortened the duration of the action potential and effective refractory period of Purkinje fibers the former was shortened more than the latter[27-29] However in cardiac muscle fibers action potential duration was only slightly reduced and the duration of the effective refractory period was lengthened[2] [illegible] The rate of rise of phase 0 was depressed more so at rapid rates at higher potassium levels and to a greater degree than with comparable amounts of lidocaine[7] Diastolic depolarization and spontaneous firing were depressed or abolished by aprindine Aprindine also reduced digitalis induced increases in potas

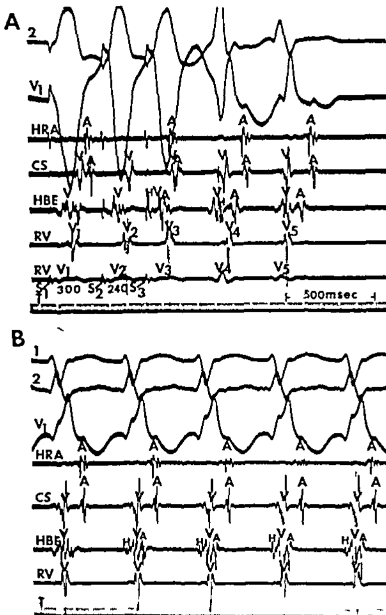


Fig 2 Initiation of intraventricular reentry and relationship to spontaneous arrhythmia ECG Leads 2 and V are shown with electrograms from the high right atrium *(HRA)* coronary sinus *(CS)* His bundle *(HBE)* and right ventricle *(RV)* In *panel A* after the eighth paced ventricular complex *(S1)* two premature stimuli (S and S) are introduced at coupling intervals of 300 (S S) and 240 (S, S) msec S results in two extra ventricular responses (V and V) which are no preceded by His potentials and which have right bundle branch block morphology and are due to intraventricular reentry (IVR) The patient s spontaneous ventricular tachycardial shown in *panel B* has a similar configuration and intracardiac activation pattern as the IVR Note "wandering retrograde His potentials *(H)* during the tachycardia

Impulses were 1 0 msec in duration and were twice diastolic threshold (≤ 3mA) The stimulation protocol included ventricular pacing at control cycle lengths ranging from 500 to 1000 msec during which single and/or double ventricular extrastimuli were delivered after every eighth paced complex The ventricular extrastimuli were delivered at progressively premature coupling intervals until ventricular refractoriness was reached

Definition of terms

S_1–S_1 was the basic paced cycle length

S and S_3 were the first and second premature stimuli delivered during an S_1 S_1

S S was the coupling interval between the

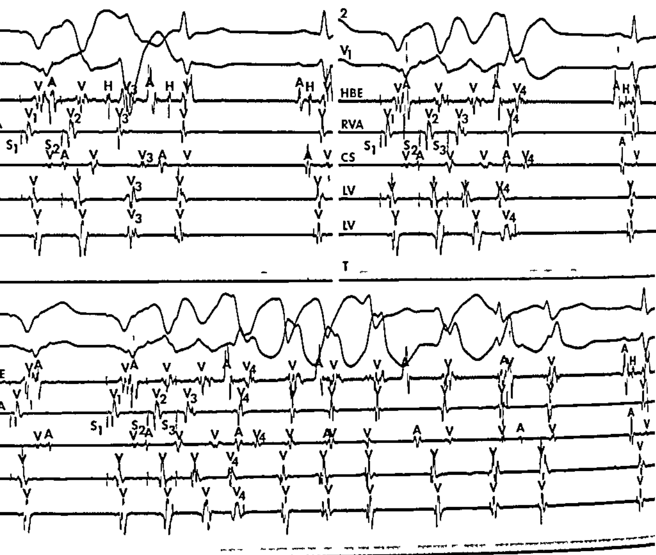


Fig 3 Bundle branch reentry and intraventricular reentry in the same patient The figure is organized from top to bottom surface electrographic Leads 2 and V and intracardiac electrograms from His bundle *(HBE)* right ventricular apex *(RVA)* coronary sinus *(CS)* two electrograms from left ventricle *(LV)* and time lines *(T)* In the *upper left panel* an RV extrastimulus *(S_)* delivered at a coupling interval of 250 msec during ventricular pacing at a cycle length of 600 msec (S S) results in a bundle branch reentrant complex *(V_3)* In the *upper right panel* a second RV extrastimulus (S) is delivered at a coupling interval of 180 msec Bundle branch reentry is abolished but a repetitive response *(V_4)* due to intraventricular reentry (IVR) results Note the difference between the IVR and paced complexes In the *lower panel* ventricular stimulation similar to the upper right panel results in an IVR identical to the one above followed by a short run of ventricular tachycardia Note the similarity between the configuration of the IVT and ventricular tachycardia complexes

ghth impulse of the basic drive cycle length to e first premature stimulus

S S_3 was the coupling interval between the st and second premature stimuli

V_1 V_2 V were the ventricular depolarizations oduced by S S and S respectively

Repetitive ventricular responses were defined single or multiple ventricular complexes that ere reproducibly induced by S or S Early sponses due to A V nodal reentry were not considered as repetitive ventricular response Two types of repetitive ventricular response were noted bundle branch reentry and intraventricular reentry (Figs 1 and 2) Bundle branc reentry was recognized by the appearance of a extra nonstimulated ventricular depolarizatio in response to S or S_3 which was dependent upo achieving a critical degree of retrograde Hi Purkinje conduction delay (V H prolongation) The QRS of this type of reentrant respon

tion IZ aprindine concentrations were initially less than 15% of NZ aprindine concentration and increased with time to approach half of NZ aprindine concentration 70 minutes after LAD occlusion Border zone aprindine concentrations were intermediate between NZ and IZ concentrations (Fig 5) Seventeen of 35 dogs (49%) receiving aprindine before LAD occlusion experienced sustained ventricular tachycardia or ventricular fibrillation compared to 5 of 34 (14%) receiving aprindine immediately after LAD occlusion ($P < 0.01$) 1 of 10 (10%) undergoing LAD occlusion without receiving aprindine ($P < 0.05$) and 0 of 16 receiving aprindine without LAD occlusion ($P < 0.01$) Aprindine administered 24 hours after coronary occlusion reduced PVCs from a mean of 35 to 12/100 beats ($P < 0.01$) The results of these studies[40] indicate that the temporal relationship between aprindine administration and LAD occlusion importantly modifies the regional myocardial distribution of aprindine and its effects on ventricular arrhythmias after coronary artery occlusion

Studies in man have demonstrated that aprindine increased the A H and H V intervals and QRS duration increased the effective refractory period of the atria and ventricles and increased the functional and effective refractory period of the A V node[1 … …]

We wish to thank Georgia Duncan for help in compiling the clinical data and Shirley Proffitt for secretarial assistance

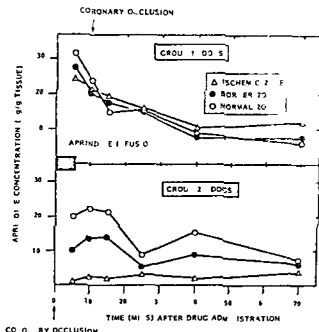


Fig 5 Regional myocardial aprindine concentrations among dogs of group 1 (given aprindine prior to coronary artery occlusion) and group 2 (aprindine after coronary artery occlusion) as a function of time after the onset of aprindine infusion Among group 2 dogs the differences between ischemic border and normal zone aprindine concentrations were all significant ($P<0.01$)

REFERENCES

1 Kesteloot H van Mieghem W DeGeest H Aprindine (AC 1802) A new antiarrhythmic drug Acta Cardiol 28 145 1973
2 Georges A Hosslet A Duvernay G Pharmacological evaluation of aprindine (AC 1802) a new antiarrhythmic agent Acta Cardiol 28 166 1973
3 Kesteloot H General aspects of antiarrhythmic treatment with aprindine Acta Cardiol Suppl 18 303 1974
4 Fasola AF Carmichael R The pharmacology and clinical evaluation of aprindine—a new antiarrhythmic agent Acta Cardiol Suppl 18 317 1974
5 Van Durme JP Rousseau M Mbuyamba P Treatment of chronic ventricular dysrhythmias with a new drug Aprindine (AC1802) Acta Cardiol Suppl 18 335 1974
6 Breithardt G Gleichmann U Seipel L Loogen F Long term oral antiarrhythmic therapy with aprindine (AC 1802) Acta Cardiol Suppl 18 341 1974
7 Bollen G Enderle J Preliminary experience in the treatment of cardiac arrhythmias with aprindine Acta Cardiol Suppl 18 355 1974
8 Besse P Giraudel JL Grosgogeat Y Haiat R Puech P Saulnier JP Traitement des troubles du rhythme par l aprindine Resultats sur 86 patients Acta Cardiol Suppl 18 389 1974
9 Hagemeijer F Janse C Hugenholtz PG Efficacite antiarythmique de l aprindine a la phase aigue de l infarctus du myocarde Acta Cardiol Suppl 18 409 19 4
10 Pouleur H Chaudron JM Reyns P Effects of disopyramide and aprindine on arrhythmias after acute myocardial infarction Eur J Cardiol 5 397 1977
11 Fasola AF Noble RJ Zipes DP Treatment of recurrent ventricular tachycardia and fibrillation with aprindine Am J Cardiol 39 903 1977
12 Troup PJ Zipes DP Aprindine treatment of recurrent ventricular tachycardia in patients with mitral valve prolapse Am Heart J 97 32? 19 9
13 Seipel L Both G Breithardt G Gleichmann U Loogen F Action of antiarrhythmic drugs in His bundle electrogram and sinus node function Acta Cardiol Suppl 18 251 1974
14 Zipes DP Gaum WE Foster PR Rosen KM Delon W Amat Y Leon F Noble RJ Aprindine treatment of supraventricular tachycardias With particular application to Wolff Parkinson White syndrome Am J Cardiol 40 586 197
15 Neuss H Schlepper M Influence of various antiarrhythmic drugs (aprindine ajmaline verapamil oxprenolol orciprenaline) on functional properties of accessory AV pathways Acta Cardiol Suppl 18 ? 9 19 4
16 Reid PR Greene HL Schaeffer AH Vargheese PJ Effects of aprindine in refractory Wolff Parkinson White syndrome Circulation 53 54(Suppl II 18) 18 19 6 (Abst)
17 Leeuwen R van Meyboom RHB Agranulocytosis and aprindine Lancet 2 1137 1976
18 Murphy PJ Metabolic pathways of aprindine Acta Cardiol Suppl 18 131 1974
19 Dodion L Suray JM de Deblecker M Georges A

ing that verapamil has little or no effect on the rapid sodium and potassium transcellular fluxes

Clinical applications

Intravenous verapamil has several important clinical applications and may be used for the following conditions (1) the treatment of coronary artery spasm (2) the treatment of hypertensive crises and (3) the treatment of supraventricular tachyarrhythmias It has also been used for such noncardiac conditions as relaxation of the uterus in threatened abortion and premature labor[2]

Treatment of coronary artery spasm There are many causes of ischemic heart disease A mechanism that has received increasing emphasis and recognition during recent years is coronary artery spasm The recognition of this mechanism has in part been due to the increasing sophistication of available techniques for demonstrating such spasm Thus coronary artery spasm is being increasingly recognized as a cause of the variant form of angina pectoris—Prinzmetal s angina [5] and its potential role in the enigma of sudden death has become especially important[6] It is interesting to note that Heberden postulated the mechanism of coronary artery spasm as early as 1768 and such medical giants as Osler[8] and Gallavardin echoed this in later years Clearly then, the advent of an important coronary spasmolytic agent is thus particularly important and especially so in the present day coronary milieu where palliative surgical coronary artery bypass is becoming an all too frequent event

The frequency of coronary artery spasm has recently received special emphasis through the elegant studies of Maseri et al by means of continuous ECG and hemodynamic monitoring they documented 8 000 to 9 000 episodes of transient acute myocardial ischemia These were reflected by S T-segment elevation or depression and T wave changes The ECG changes occurred within minutes of the onset of pain but could also occur in the absence of pain They also showed that spasm could occur in apparently normal coronary arteries and lead to S T-segment elevation to be followed shortly thereafter by deeply inverted T waves During the phase of T wave inversion these patients usually developed ventricular tachycardia which sometimes progressed to ventricular fibrillation and sudden death The only way these episodes of ventricular fibrillation could be prevented was by treating the symptom i e the relief of the vasospastic angina pectoris and not by the administration of antiarrhythmic drugs They conclude that preventing angina meant preventing ventricular fibrillation in these cases This observation is of particular significance since it heralds an entirely new therapeutic approach And in this respect verapamil is highly effective by both the oral route[9] and the intravenous route[11] in abolishing ameliorating and preventing coronary vasospastic attacks as reflected by angina of effort angina at rest and in particular Prinzmetal s angina

Treatment of hypertensive crises Hypertensive crises respond dramatically to the administration of intravenous verapamil[1 1] Blood pressure control is usually achieved within 1 to 2 minutes following the intravenous injection of 5 mg of verapamil The effect is due to a reduction in peripheral vascular resistance and is in no way related to any negative inotropic effect In this respect it is important to note that intravenous verapamil does not reduce normal blood pressure or at most has only a negligible and unimportant effect

Treatment of supraventricular tachyarrhythmias Intravenous verapamil was first used for the treatment of arrhythmias in the late 1960s and my experience with this agent both on an investigational basis and in routine clinical practice now involves many hundreds of cases and extends over a decade Most of these patients had grade IV cardiac failure and received digitalis therapy This experience has left me with no doubt whatsoever that verapamil is the best available pharmacologic agent for rapid action in affecting A V nodal delay or block This property is of particular value in interrupting the conduction circuit of a reciprocating tachycardia and thereby terminating the attack Note that it makes no difference which anatomic bypass is used in the reciprocal circuit—a James bypass an intranodal pathway a Kent bundle or a Mahaim fiber—since termination is effected by block within the A V nodal part of the circuit and not within the bypass

The Investigators Brochure of the Knoll Pharmaceutical Company reflects a review of 134 studies involving the use of intravenous verapa

Characteristiques pharmacocinetiques et biodegradation de l aprindine chez l homme Therapie 29 221 1974
20 Gerin M Gerin Y Duvernay G Georges A Effects of aprindine (AC 1802) on cardiac function in conscious dogs. Acta Cardiol Suppl 18 143 1974
21 Mertens HM Neuhaus KL Investigation on the cardio vascular effects of aprindine Acta Cardiol Suppl 18 163 1974
22 Verdouw PD Remme WJ Hugenholtz PG Cardiovascu lar and antiarrhythmic effects of aprindine (AC 1802) during partial occlusion of a coronary artery in the pig Cardiovasc Res 11 317 1977
23 Remme WJ Verdouw PD Cardiovascular effects of aprindine A new antiarrhythmic drug Eur J Cardiol 3 307 1975
24 Rousseau MF Brasseur LA Detry JM Hemodynamic effects of aprindine during upright exercise in normal subjects Acta Cardiol Suppl 18 195 1974
25 Besse P Choussat A Effects de l aprindine (AC 1802) sur la fonction myocardique chez l homme Acta Cardiol Suppl 18 217 1974
26 Piessens J Willems J Kesteloot H DeGeest H Effects of aprindine on left ventricular contractility in man Acta Cardiol Suppl 18 203 1974
27 Carmeliet E Verdonck F Effects of aprindine and lidocaine on transmembrane potentials and radioactive K efflux in different cardiac tissues Acta Cardiol Suppl 18 73 1974
28 Verdonck F Vereecke J Vleugels A Electrophysiologi cal effects of aprindine on isolated heart preparations Eur J Pharmacol 26 338 1974
29 Steinberg MI Greenspan K Intracellular electrophysio logical alterations in canine cardiac conducting tissue induced by aprindine and lidocaine Cardiovasc Res 10 236 1976
30 Elharrar V Bailey JC Lathrop DA Zipes DP Effects of aprindine HCl on slow channel action potentials and transient depolarizations in canine Purkinje fibers J Pharmacol Exp Ther 205 410 1978
31 Gilmour RF Chikharev DG Jurevichus J Zacharov S Zipes DP Effects of aprindine on transmembrane cur rents and contractile force in frog atria Circulation 59 60(Suppl II) 209 1979 (Abst)
32 Elharrar V Foster PR Zipes DP Effects of aprindine HCl on cardiac tissues J Pharmacol Exp Ther 195 201 1975
33 Kulbertus H Collignon P Action des anti arythmiques sur la conduction intracardiaque Acta Cardiol Suppl 18 241 1974
34 Kroll DA Lucchesi BR Antiarrhythmic and antifibrilla tory properties of aprindine J Pharmacol Exp Ther 194 427 1975
35 Ueda M Kimoto S Matsuda S Kawakami M Morishi e E Matsumura S Takeda H Antiarrhythmic effects of aprindine on several types of ventricular arrhythmias. Jpn J Pharmacol 25 549 1975
36 Foster PR King RM Nicoll AB Zipes DP Suppression of ouabain induced ventricular rhythms with aprindine HCL A comparison with other antiarrhythmic agents. Circulation 53 315 1976
37 Zipes DP Elharrar V Noble RJ Gaum WE Troup PJ Fasola A Effects of various drugs on ventricular conduc tion delay and ventricular arrhythmias during myocar dial ischemia in the dog *In* Kulbertus HE editor Re-entrant arrhythmias London 1977 MTP Press, p 312
38 Elharrar V Gaum WE Zipes DP Effect of drugs on conduction delay and incidence of ventricular arrhyth mias induced by acute coronary occlusion in dogs Am J Cardiol 39 544 19
39 Gaum WE Elharrar V Walker PD Zipes DP Influence of excitability on the ventricular fibrillation threshold in dogs Am J Cardiol 40 929 1977
40 Nattel S Pedersen DH Zipes DP Alterations in regional myocardial distribution and antiarrhythmic effects of aprindine produced by coronary artery occlusion in the dog Cardiovasc Res (In press)
41 Schlepper M Neuss H Changes of refractory periods in the AV conduction system induced by antiarrhythmic drugs A study using His bundle recordings Acta Cardiol Suppl 18 269 1974

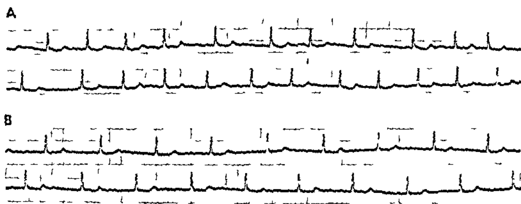


Fig 1 A Section of the control tracing (continuous strip of standard lead II) showing atrial fibrillation with irregular ventricular response B Tracing recorded after the administration of intravenous verapamil shows regularization of the ventricular response

mil for the treatment of various arrhythmias There were 4 379 documented arrhythmic episodes treated with intravenous verapamil some of which are considered in further detail below

Supraventricular tachycardia The Knoll review reflects 1 607 published episodes of supraventricular tachycardia treated with intravenous verapamil Of these 1 307 (81%) were converted to normal sinus rhythm and 139 (9%) reflected a significant reduction in rate The precise mechanism of the supraventricular tachycardia however was not always certain and no distinction in this analysis could therefore be made between ectopic atrial supraventricular tachycardia and reciprocating tachycardia Such distinction however is very important in the evaluation of this drug Thus my experience comprises 59 cases of the reciprocating form of supraventricular tachycardia Eighteen of these cases involved retrograde conduction through a Kent bundle one was associated with anterograde conduction through a Kent bundle and two were associated with retrograde conduction through a Mahaim fiber The precise anatomic substrate for the circus movement could not be determined in the remaining 38 cases although the diagnosis of reciprocating tachycardia was clear The reciprocal circuit could have involved an intranodal bypass a James bypass or retrograde conduction through a Kent bundle or Mahaim fiber The reciprocating tachycardia was terminated with conversion to normal sinus rhythm in all 59 cases (100%)

Atrial flutter The Knoll review reflects 343 documented episodes of atrial flutter treated with intravenous verapamil Of these 31% were converted to normal sinus rhythm and a significant reduction of the ventricular response was obtained in 186 (54%) My experience comprises 87 patients with atrial flutter all of whom had a reduction in ventricular response Thirteen (15%) of these subsequently converted to normal sinus rhythm Eleven (13%) converted to atrial fibrillation two of which subsequently converted to normal sinus rhythm

Atrial fibrillation The Knoll analysis reflects a total of 1 474 documented episodes of atrial fibrillation treated with intravenous verapamil Of these 230 (16%) were converted to normal sinus rhythm and a significant rate reduction was obtained in 1 149 (78%) The data include my own investigational experience of 115 cases[7, 17] Of these 115 cases, a reduction in ventricular response was obtained in 111 (97%) The higher the initial control rate the higher the ensuing reduction following the administration of intravenous verapamil There was also a diminution in the amplitude of the fibrillating deflections in 44% of cases In contrast to other studies in which conversion to sinus rhythm was obtained in a moderate number of cases there was no conversion to sinus rhythm in the studies of Schamroth et al[6, 7] A possible reason for this was the advanced state of disease and the marked associated cardiomegaly in most of these patients

A noteworthy feature was an associated regularization of the ventricular response in most of these patients This occurred in the presence of continuing atrial fibrillation and in the absence of complete A V block[6] (Figs 1 and 2)

Amiodarone in the treatment of cardiac arrhythmias in children One hundred thirty five cases

Philippe Coumel M D and Jean Fidelle M D *Paris and Les Loges en-Josas France*

Oral amiodarone was g ven to 135 children (mean age 10 2 years) for a mean duration of 4 1 months (range 1 day to 6 years) for mainly id opathic (25 /) and postoperative (61 ʹ) arrhythm as Complete ECG control or partial ECG control with cl nical improvement was obtained in 60 / and 33% of cases respectively regardless of the arrhythmia location (atrial 69% junctional 16% and ventricular 15 /) mechanism resistance (55 /) or sensitivity (45 %) to other drugs and presence of card omegaly (40) or clin cal signs of heart failure (27 /) The only factor favoring improvement was a short history (< 2 months in 54 %) The rapid onset of drug effect (4 1 days) the early relapses after treatment discontinuation (3 3 weeks) and the absence of side effects due to drug accumulation reflect a faster metabolism than that in adults with no cardiac tox city and a low incidence of thyro d dysfunct on (2 hyperthyroid 1 hypothyroid)

Two factors are responsible for the greater difficulty in treating arrhythmias in children compared to adults (1) the many different types of arrhythmias some of which are refractory and peculiar to children and (2) the limitations of therapeutic choice due to greater drug toxicity This is why amiodarone is a considerable therapeutic asset in children We report here our experience since 1971

Material and methods

The study includes 135 children (80 boys and 55 girls) ages 0 to 15 years (Fig 1) treated and followed up from 1971 to 1979 and also includes a previously published study[1] of 50 patients The diagnosis and cause of the arrhythmias are detailed in Tables I and II The predominance of atrial (69%) and postoperative arrhythmias (61%) is emphasized as well as some resistant arrhythmias such as permanent reciprocal tachycardia[2] congenital ectopic His bundle tachycardia[3] (Figs 2A and 2B) and catecholamine ventricular tachycardias (Fig 3)

The arrhythmias were accompanied by clinical cardiac failure in 27% isolated radiologic cardiomegaly in 40% and were well tolerated hemodynamically in only 33% of the cases The arrhythmias were chronic (lasting more than 2 months) in almost half of the cases (46%) In over half (55%) the arrhythmias were resistant to the various antiarrhythmic drugs used in children i.e digitalis disopyramide beta blockers atropine and verapamil Among the remaining patients some had no treatment other than amiodarone because they had well known resistant arrhythmias

The initial treatment was a daily oral dose of 800 mg of amiodarone adjusted according to the child s surface area This dose was maintained for an average of 2 weeks then reduced by half and was finally given 5 days out of 7 Because of our adult experience and the large predominance of supraventricular arrhythmias most of the patients were also digitalized Digitalization was always achieved before amiodarone was given in cases of cardiac failure and was associated with a diuretic In a small number of cases (eight patients) one single dose of amiodarone was given

From th Hop t l Lariboisiere Paris, and Chat u des Cotes, Les Loges-en-Josas Fra e

Reprint requests P C umel, M D H pit l Lariboisi re 2 rue Ambroise-Pare 75010 Paris, France

0002-8703/80/131063 + 0 $00 70/0 © 1980 The C V Mosby Co

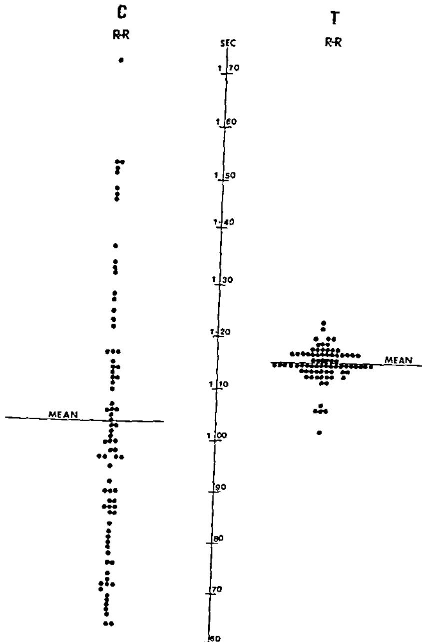


Fig 2 ~ win, the "regularization of the ventricular rhythm C = scatter of the R R intervals in the contr ig atter of the R R intervals in the second test tracing

The mechani m of the egularizing effect is uncertain It is unlikely to b due to the development of complete A bl ck with A V nodal escape rhythm since th e ape rhythm is too fast and some irregularity i till present It may result from a stabilizing effect on the varying degrees of concealed A V nodal conduction which may cause the irregular ventricular response in atrial fibrillation—perhaps by increasing the absolute but not relative refractory period An activation front approaching the atrioventricular node from the direction of the SA node is well transmitted whereas a front approaching from other directions may be delayed or blocked Verapamil may stabilize the chaotic atrial activation front

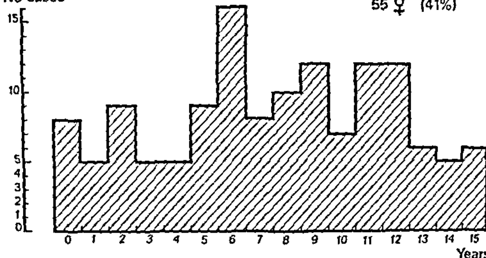


Fig 1 Age and sex distribution of the 135 patients

Table I Arrhythmia diagnosis (n = 135)

Type	*No of cases*	%
Atrial	7	5
Sinus tachycardia		
Coronary sinus rhythm	1	1
Extrasystole	31	23
Ectopic tachycardia	43	32
Flutter fibrillation	4	3
Bradycardia tachycardia syndrome	7	5
Total	93	69%
Junctional	7	5
Permanent reciprocating tachycardia		
Paroxysmal reciprocating tachycardia (WPW)	8	6
His tachycardia	7	5
Total	22	16%
Ventricular	15	11
Extrasystole		
Ventricular tachycardia	1	1
Catecholamine induced ventricular tachycardia	4	3
Total	20	15%

WPW = Wolff Parkinson Whit[illegible] syndrome

to terminate attacks of supraventricular tachycardia and the treatment was discontinued after it was successful We have no experience with the intravenous route in childhood

The rate monitoring was a [illegible] based on heart rates taken every 2 h[illegible] and night and included several daytime a[illegible] nighttime ECG

Table II Etiology of arrhythmias

Etiology
Idiopathic
Congenital cardiopathies
Preoperative
Postoperative
Wolff Parkinson White syndrome
Valvular diseases
Cardiomyopathies

controls many of which had at le[illegible] at normal recording speed with st[illegible] cation and then at double these [illegible] the drug s usual effect on the slov[illegible] monitoring was progressively sp[illegible] term treatment in nonhospitalize[illegible]

The mean treatment period w[illegible] (range 1 day to 6 years) For [illegible] treatments the follow up in[illegible] weight psychomotor developme[illegible] state and serum levels to detect [illegible] roid dysfunction (cholesterol [illegible] Hamolsky test)

Results

The results were considered go[illegible] sinus rhythm was reestablished a[illegible] cardiac rate was reduced but the [illegible] not perfectly controlled on the [illegible] when the treatment clinically an[illegible]

This regularization effect has recently also been noted following the administration of large doses of oral verapamil[1]

Ventricular tachycardia The Knoll analysis reflects a total of 239 documented episodes of ventricular tachycardia treated with intravenous verapamil Of these 239 episodes 157 (66%) were apparently converted to normal sinus rhythm This contrasts with my own experience in which no effect was noted in ten cases of extrasystolic ventricular tachycardia and I have stopped using verapamil for this purpose This difference in experience may be due to the fact that here again the precise mechanism of the ventricular tachycardia was delineated Thus for example an idioventricular tachycardia will be abolished if its rate is slowed relative to the sinus rate Extrasystolic ventricular tachycardia will not be affected in this way

Contraindications

Verapamil is a safe drug provided certain basic contraindications are heeded The drug should not be administered under the following circum stances cardiogenic shock any degree of A V block structural nodal disease (the so called sick sinus syndrome) hypotension (except where due to a tachyarrhythmia as such) and in association with beta blocking agents or disopyramide

Comments Verapamil should also be used with caution in the presence of intraventricular con duction defects

The so called sick sinus syndrome is an unfor tunate term for it is abundantly clear that it is not only the sinus node which is so to speak sick but also the A V node and its appendages Struc tural nodal disease is preferred since it connotes a widespread disease process involving the con ducting system Verapamil is contraindicated when any manifestation of this syndrome is evi dent

The negative inotropic effect Verapamil has a slight negative inotropic effect which is usually insignificant This is more than counterbalanced by the reduction in the peripheral resistance and the reduction in cardiac work resulting from the diminution in the afterload as indicated by Fer linz et al

The question of adverse side effects

I have had no deaths or adverse effects in any of my patients Four deaths following the adminis tration of verapamil have been reported in the world literature The circumstances in all these cases however were either bizarre and/or clear contraindications were present Thus (1) The case reported by Sacks and Kennelly[1] was that of a 63 year old man in *cardiogenic shock* and who also had *bifascicular block* one (2) The case reported by Witchitz et al was a 63 year-old woman with *sarcoma of the heart* (3) The case reported by Apitz and Gaismarer[3] was that of a 10 year old boy with *fibroelastosis* who had *first to third degree A V block* (4) The case reported by Heck et al[4] was that of a 57 year old man who was seriously ill with myocardial infarction and in whom *digitalis and verapamil* were administered intravenously *within a few minutes of each other*

Conclusions

Verapamil the pioneer of calcium ion antagon ists represents an important milestone in clinical therapy Its present status in cardiologic practice is that of significant benefit in three important conditions

It stabilizes and slows or blocks conduction in the A V node and is the drug of choice for action on this structure It has an important coronary spasmolytic action where its full potential has not as yet been realized Its reduction of periph eral vascular resistance is important in the treat ment of hypertension And intravenous adminis tration is of particular value in dealing with crises related to these situations The reduction in cardiac afterload also has a beneficial effect on the ailing heart

The future will see expansion of clinical appli cation to other clinical disciplines where smooth muscle relaxation is the therapeutic aim Verap amil thus heralds an exciting new era a new dimension in therapeutic approach

I wish to thank the Photographic Unit Department of Medicine University of the Witwatersrand for the photo graphic reproductions.

REFERENCES

1 Singh BN Vaughan Williams EM A fourth class of antidysrhythmic action? Effect of verapamil on ouabain toxicity on atrial and ventricular intracellular potentials, and on other features of cardiac function Cardiovasc Res 6 109 1972
2 Weidinger H Wiest W Treatment of premature labor with a n w uterus relaxing agent and Isoptin Fortschr Med 89 1380 1973
3 Meller J Pichard A Dack S Coronary arterial spa m in

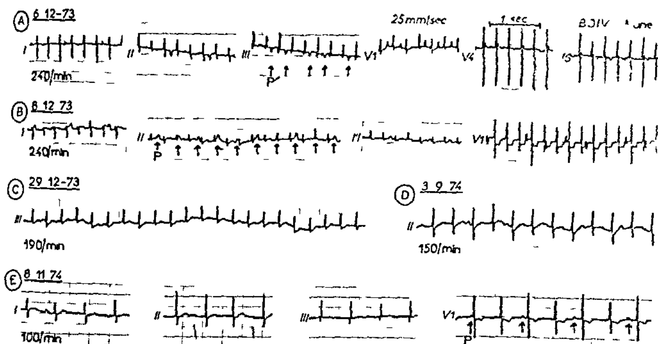


Fig 2A Resistant His bundle tachycardia in a 1 month old infant The cardiac insufficiency (see Fig 2B) is clearly related to the supraventricular tachycardia in this infant a cousin of whom died several years earlier from the same tachycardia after all antiarrhythmics had failed (amiodarone had not been tried) Tracing *A* (Dec 6 1973) clearly shows the narrow QRS complexes with a second degree ventriculoatrial block (arrows point to retrograde P' waves) Two days later (tracing *B*) the A V dissociation is complete Tracings *C* to *E* were taken during the following 11 months and show the progressive slowing of the ectopic focus with a persistent A V dissociation

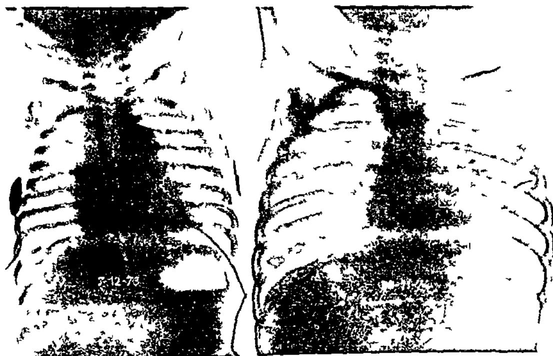


Fig 2B Dramatic regression of the cardiomegaly with the progressive slowing of the tachycardia in patient in Fig 2A This case is classified as an average result (clinical but no ECG control of the arrhythmia)

Prinzmetal s angina A proved hypothesis Am J Cardiol 37.938 1976
Parodi O Severi S Maseri A Biagini A Reversible reduction of regional myocardial blood flow as a cause of primary angina at rest Relation hip with electrocardiographic S T changes *In* Klassen GA Lesch M editors Primary and secondary angina pectoris New York 19 8 Grune & Stratton Inc pp 227 237
Maseri A L Abbate A Baroldi G Chierchia S, Marzilli M Ballestra A M Severi S Parodi O Biagini A Distante A Pesola A Coronary vasospasm as a possible cause of myocardial infarction N Engl J Med 299 1271 1978
Maseri A L Abbate A Chierchia S Parodi O Severi S Biagini A Distante A Marzill M Ballestra AM Significance of spasm in the pathogenesis of ischemic heart disease Am J Cardiol 44 788 1979
Heberden W Some account of a disorder of the breast Med Trans Coll Physicians (Lond) 2 59 1768
Osler W Lumleian lectures on angina pectoris. Lancet 1 697 1910
Gallavardin L Les syncopes d effort Lyon Med 151 217 1933
Parodi O Maseri A Simonetti I Management of unstable angina at rest by verapamil Br Heart J 41 167 1979
Piccolo E Verapamil in the therapy of acute coronary insufficiency Atti Giornata Cardiol 2 10 1977
Lewis GRJ Morley KD Lewis BM Bones PJ The treatment of hypertension with verapamil NZ Med J 87 351 1978
Bender F Treatment of tachycardic arrhythmias and arterial hypertension with verapamil Arzneim Forsch 20 1310 1970
14 Hagino N Application of Iproveratril in the pharmo therapy of hyperten ion Jpn J Clin Exp Med 45 208 1968
15 Verapamil clinical information Investi ators s brochure Knoll Pharmaceutical Feb 1977
16 Schamroth L Immediate effects of intravenous verapamil on atrial fibrillation Cardiovasc Res 5 419 1971
17 Schamroth L, Krikler DM Garrett C Immediate effects of intravenous verapamil in cardiac arrhythmias Br Med J 1 660 197
18 Khalsa A Olsson SB Verapamil induced ventricular regularity in atrial fibrillation Acta Med Scand 205 509 19 9
19 Schamroth L Disorders of cardiac rhythm, ed 2 Oxford 1980 Blackwell Scientific Publications
20 Ferlinz J Easthope JL, Aronow WS Effects of verapamil on myocardial performance in coronary disease Circulation 59 313 1979
21 Sa ks H Kennelly BM Verapamil in cardiac arrhythmias Br Med J 2 716 1972
22 Witchitz S Haiat R Tarrade T Chiche P Accidents cardiovasculaires au cours des traitements par le verapamil A propos de 6 observations Nouv Presse Med 4 337 1975
23 Apitz J Gaissmarer U Zwischenfall mit todlichem ausgang nach intravenoser injektion von Isoptin Med Klin 66 701 1971
24 Heck von J Heim RR Elbers C Letaler ausgang nach intravenous behandlung mit Isoptin Z Kreislforsch 61 621 1972

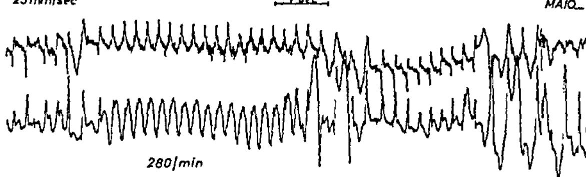


Fig 3 Catecholamine related severe ventricular tachycardia in an 8 year old boy A strip from the Holter monitoring clearly shows the mechanism of the Adams Stokes syndrome very rapid and polymorphic attacks of ventricular tachycardia and fibrillation are readily induced by exercise Beta blockers were only partially effective and a new 6-year treatment with amiodarone did control the arrhythmia

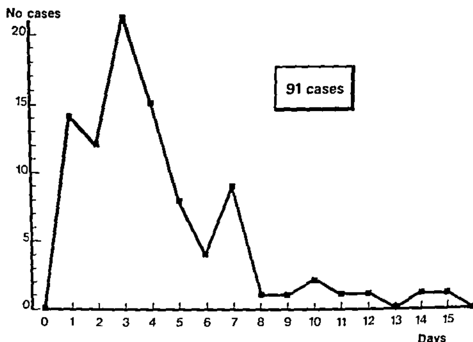


Fig 4 Delay before response to amiodarone treatment In 91 patients in whom the delay could be precisely evaluated the great majority (83) responded during the first week of treatment (one fourth at the third day) This is in contrast to the necessary 7 to 10 day impregnation in adults

graphically was ineffective The results were good in 81 cases (60%) average in 44 (33%) and poor in only 10 (7%) i e more than 90% of the cases totally or partially improved The cause of the arrhythmia its mechanism (ectopic focus or reentry) localization (Table III) and resistance to other antiarrhythmics (Table IV) do not affect drug efficacy (Pearson chi square test) although a longer duration of the arrhythmia (greater than 2 months) resulted in less drug effectiveness ($P < 0\ 10$)

The delay before response to treatment coul be evaluated in 91 patients and is represented i Fig 4 It ranges from 1 to 16 days and its mea value is 4 1 days with a peak at day 3 In eigh cases of supraventricular tachycardia a full sin gle dose of oral amiodarone was given and rhythm reduction was obtained between 5 and 7 hours i seven patients and after 24 hours in one

Conversely the delay before relapses afte interruption of treatment could be assessed in 3 cases of serious chronic and recurring arrhyth

Hemodynamic and electrophysiologic interactions between antiarrhythmic drugs and beta blockers, with special reference to tocainide

Hamid Ikram M D *Christchurch New Zealand*

The administration of beta receptor blocking drugs and antiarrhythmic drugs in close proximity may result in hemodynamic electrophysiologic or pharmacokinetic interactions We examined the hemodynamic and electrophysiologic effects of 0 20 mg/kg intravenous metoprolol followed by a 15 minute infusion of 0 75 mg/kg/min tocainide In the six patients studied metoprolol produced a fall in cardiac rate and output which was not further altered by tocainide Both drugs decreased peak left ventricular (LV) dP/dt ejection fraction and mean V_{cf} There was no change in LV end-diastolic pressure or echo dimension and in clinical ill effects In eight patients without sinus or A V nodal disease electrophysiologic studies showed mild depression of A V conduction by metoprolol Tocainide depressed s nus node function and shortened the functional refractory period of the His Purkinje system There were no cl nical sequelae However three patients with preexisting electrophysiologic abnormalities developed asystole There was no evidence of pharmacokinetic interaction It is concluded that metoprolol and tocainide can be given concurrently with reasonable safety to cardiac patients without electrophysiologic abnormalities

Antiarrhythmic drugs are frequently given con currently with beta adrenoreceptor drugs pre scribed for angina hypertension or arrhythmias Such combinations may result in serious adverse effects from drug interactions These are of three types

First there is hemodynamic interaction This was exemplified by the development of circula tory collapse after intravenous verapamil had been given to a patient already on propranolol[1] Another patient in this series with Wolff Parkin son White syndrome developed cardiogenic shock when propranolol was added to the vera pamil therapy which was already being adminis tered Seabra Gomes et al showed that when intravenous practolol and verapamil were given individually to patients whose heart rates had been fixed with atrial pacing there was little hemodynamic alteration However the adminis

From the Department of C d ology The Prin s M rg t Ho p t l Chri tchurch, New Zealand

Reprint requests Hamid Ik m M D Chi f f C d l g Th Princess Margaret Hospital Christchu h, New Ze l d

tration of the two drugs together resulted in pronounced fall in cardiac output They advis caution in the combined use of these drugs patients with impaired myocardial function

Second drug interactions may depress elect cal activity Asystole has been reported in t patients on beta blockers who were given intr venous verapamil[1] Both of these patients h normal A V conduction Patients with impair A V conduction or the sick sinus syndrom should be treated with great caution with comb nations of verapamil and beta blockers

Serious electrophysiologic side effects ha been reported with combinations of disopyram and beta blocking drugs Gelipter and Ha e reported severe bradycardia and no effective ca diac output in a 56 year old man with myocardi infarction who was being treated with disopyram ide and who had previously been given pract lol

Cumming and Robertson reported two cases supraventricular tachycardia in which seve hypotension and bradycardia occurred wh practolol and disopyramide were used togeth

0002 8703/80/1310 6 + 05$00 50/0 © 1980 The C V Mosby C

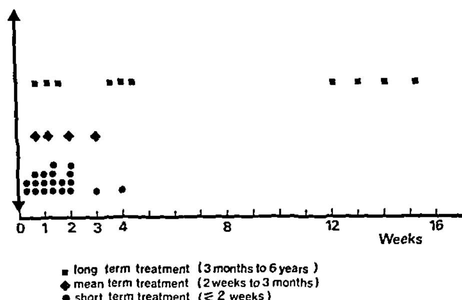


Fig 5 Delay before relapse of chronic arrhythmias after cessation of treatment In 34 patients in whom the recurrence of the arrhythmia could be evaluated it occurred within 2 weeks in 24 after 3 to 4 weeks in six and after 12 to 16 weeks in four

mias (Fig 5) Its mean value was 3 3 weeks and in 24 cases it was 2 weeks or less The duration of treatment and child s age affect the delay before relapse In 10 treatments lasting between 3 months and 6 years relapses occurred three times in 2 weeks three times in 4 weeks and four times in 2 to 3 months

Concerning children and long term treatments particular attention must be paid to drug tolerance Electrocardiographically repolarization changes must occur before a treatment failure is accepted i e before the appearance of increased height of U waves and lengthening of the Q T segment The sinus rate was steadily reduced but in only 10 cases was it less than 60/min at rest and in seven of these patients there was a preexisting atrial rhythm disturbance The three cases of sinoatrial block were preexisting We observed no intra atrial conduction disturbances The P R lengthening was from 40 to 80 msec in 41 cases with Wenckebach periods in three cases We observed no distal A V conduction disturbance in spite of 52 cases of complete right bundle branch block 15 of which were associated with a left anterior hemiblock The QRS duration increased by 20 to 40 msec in two cases of incomplete right bundle branch block

Corneal deposition (three cases) photosensitivity (four cases) and bluish skin coloring (one case after 72 months of treatment) were rarely observed and only in older children In four cases

Table III Amiodarone efficacy according to localization of arrhythmias

	Atrial		*Junctional*		*Ventricular*	
Results	*93 cases*	*69%*	*22 cases*	*16%*	*20 cases*	*15%*
Good (81 cases 60%)	55 cases	41%	12 cases	9%	14 cases	10%
Fair (44 cases 33%)	31 cases	23%	10 cases	7%	3 cases	2%
Poor (10 cases 7%)	7 cases	5%	0 cases		3 cases	2%

Table IV Amiodarone efficacy according to resistance to prior treatment

	Prior treatments ineffective		*Amiodarone as first treatment*	
Results	*4 cases*	*55%*	*61 cases*	*45%*
Good (81 cases 60%)	41 cases	30%	40 cases	30%
Fair (44 cases 33%)	30 cases	23%	14 cases	10%
Poor (10 cases %)	3 cases	2%	7 cases	5%

nightmares hallucinations and personality problems caused the cessation of treatment These signs seemed to be precursors of hyperthyroidism in two other cases they appeared before obvious biologic modifications Conversely one patient developed hypothyroidism which may have reflected a predisposition (control cholesterol

Table I Hemodynamic results (mean ± 1 SD)

Data	*Control*	*Immed after metoprolol*	*15 min after metoprolol*	*Immed after tocainide*	*15 min after tocainide*
Heart rate/min	79 ± 13	68 ± 15	66 ± 15	68 ± 14	67 ± 15
	P < 0 01 (Control vs Immed after metoprolol)				
	P < 0 01 (Control vs 15 min after metoprolol)				
Cardiac index (L/min/m)	3 49 ± 1.53	2 97 ± 1 77	2 80 ± 1 64	2 2 ± 1 28	2.21 ± 1.3
	P < 0 05 (Control vs Immed after metoprolol)				
		P < 0 01 (Control vs 15 min after metoprolol)			
LV max dP/dt (mm Hg sec)	1 510 ± 375	1 378 ± 373	1 246 ± 304	992 ± 27	1 027 ± 328
	P < 0 65 (Control vs Immed after metoprolol)			*P* < 0 01 (15 min after metoprolol vs Immed after tocainide)	
		P < 0 01 (Control vs 15 min after metoprolol)			*P* < 0 001 (15 min after metoprolol vs 15 min after tocainide)
LV stroke work index (gm/beat/m)	64 9 ± 33 2	59 2 ± 31 9	58 1 ± 31 5	44 6 + 25.2	42 9 ± 26.9
				P < 0 05 (15 min after metoprolol vs Immed after tocainide)	
				P < 0 05 (15 min after metoprolol vs 15 min after tocainide)	
LV end-diastolic pressure (mm Hg)	24 ± 9	25 ± 10	25 ± 9	24 ± 8	26 ± 7
Mean pulmonary artery "wedge pressure (mm Hg)	16 ± 8	17 ± 8	18 ± 8	22 ± 8	23 ± 8
Mean pulmonary artery pressure (mm Hg)	23 ± 10	23 ± 9	22 ± 10	27 ± 10	27 ± 10
				P < 0 05 (15 min after metoprolol vs Immed after tocainide)	
End diastolic dimension (cm)	6 2 ± 1 4	6 1 ± 1 3	6 1 ± 1 0	6 4 ± 1 1	6 5 ± 1 0
Echo ejection fraction (%)	62 ± 16	60 ± 12	53 ± 15	52 ± 16	44 ± 13
		P < 0 01 (Control vs 15 min after metoprolol)			< *P* 0 01 (Immed after tocainide vs 15 min after tocainide)
Mean V (circ/sec)	0 78 ± 0 19	0 73 ± 0 16	0 64 ± 0 17	0 5 ± 0 06	0 48 ± 0 04
		P < 0 01 (Control vs 15 min after metoprolol)			*P* 0 05 (Immed after tocainide vs 15 min after tocainide)

One of these patients died The other developed a further episode of supraventricular tachycardia which was treated without untoward effect by disopyramide alone This suggests that it is the combination rather than the individual drug that leads to problems The combined use of beta blockers and disopyramide is relatively contraindicated.

Amiodarone a new antiarrhythmic drug has also been reported to cause asystole and severe bradycardia when given in close proximity to propranolol Asystole and depression of myocardial contractility have also been reported with propranolol therapy for digitalis toxicity This complication is frequent enough to preclude beta blocker treatment for digitalis toxicity unless everthing else has failed

A third type of interaction is where one drug interferes with the pharmacokinetics of another Administration of propranolol reduces the clearance of lidocaine and quinidine

We studied the hemodynamic electrophysiologic and pharmacokinetic effects of tocainide in patients who were given intravenous metoprolol shortly before tocainide

Material and methods

Hemodynamic interactions of tocainide Hemodynamic observations were made on six patients five men and one woman undergoing routine diagnostic catheter studies A Swan Ganz catheter was positioned in the pulmonary artery for measurement of pressure and thermal dilution cardiac output The left ventricular pressure was measured by means of a Millar catheter tip manometer Left ventricular dimensions were recorded simultaneously by M mode echocardiography Following control measurements metoprolol was infused in a dose of 0 20 mg/kg over a 5 minute period Hemodynamic and echo measurements were recorded at the end of the infusion and 15 minutes later Tocainide was then infused in a dose of 0 75 mg/kg/min over a 15 minute period Hemodynamic measurements

2 60 gm/L) In these three patients the thyroid dysfunction (two hyperthyroid one hypothyroid) completely regressed in several weeks with cessation of treatment Biologic surveillance confirms the rarity of thyroid complications in the present experience plasma cholesterol levels Hamolsky test T_3 T and TSH were monitored before and after a mean duration of 14 5 months of treatment in 40 patients No variation exceeding the normal range for these tests was observed except in the three previously mentioned patients

Discussion

After amiodarone has been used for more than 10 years as an antiarrhythmic in adults, it is not necessary to emphasize its effectiveness and uniqueness However its overall effectiveness does not replace other antiarrhythmics and moreover its problems of tolerance or thyroid toxicity should not make it an initial simple therapeutic approach These side effects were carefully considered before this drug was used in children and only its extraordinary effectiveness and the observed excellent tolerance encouraged us to increase its use over the 9 year period We know of only one equivalent experience (Kreutzer BA Personal communication)

Amiodarone cured or improved arrhythmias in six out of ten patients and improved their tolerance in three out of four remaining patients whatever the mechanism localization and previous resistance This is without evidence of poor tolerance or nonreversible toxicity and represents almost all the desirable properties for an ideal antiarrhythmic It is mostly on a matter of principle that one should not use this as the first medication in childrens rhythm disturbances even though it is more consistently effective and better tolerated than in adults

The drug is metabolized more rapidly in children with the onset of action in 4 days instead of 10 days as in adults and effectiveness after cessation lasts less than a few weeks as opposed to several months in adults These are the norms found in animal experiments from which we also know that the drug concentration in the adipose tissue and muscle is 10 to 30 times greater than in the plasma There is no plasma assay to regulate the dosage used in a clinical setting and in any case the tissue binding might invalidate normal pharmacokinetic parameters and should not be interpreted as rigorously as for other drugs The fact that children have less adipose tissue than adults may account for the faster metabolism in the former but probably this is not the only difference and does not explain the unique phenomenon of corneal deposits in adults The drug s primary and secondary effects obviously vary with age and this is clearly visible in the older child who tends to react as an adult

It is in this regard that the younger the child and the more recent the arrhythmia the more oral amiodarone is likely to be an effective emergency treatment able in a few hours to terminate a reciprocal junctional paroxysmal tachycardia or an atrial or ventricular tachycardia while avoiding the dangers of other antiarrhythmics The mechanism of action of amiodarone is clearly known and it reduces the outward potassium current as well as the rapid inward sodium current without being classed as a membrane stabilizing agent Also it is not a beta blocker but nevertheless slows the beta response[6] Finally it has no effect on the slow calcium canal and its essential action is to lengthen the duration of the action potential and refractory period A single mechanism of action seems to fit poorly with the drug s widespread effectiveness in a great many different arrhythmias It is rare to combine amiodarone with other antiarrhythmics with the exception of digitalis whose supraventricular antiarrhythmic action is synergic In addition digitalis alone can compensate for amiodarone s real although moderate depressive myocardial effect[7]

The demonstration of wide clinical efficacy does not dictate indications for medication However one can recognize cases in which one should directly resort to this treatment In practice this applies to all poorly tolerated arrhythmias, as it is the least dangerous in the presence of poor myocardium In the long run it does not necessarily have to be maintained except in special resistant life or death childhood arrhythmias as such certain long term atrial tachycardias, chronic reciprocal tachycardias ectopic focus tachycardias in infants and catecholergic ventricular tachycardias when not controlled by beta blocking treatment

REFERENCES

1 Fidelle JE Attuel P Tournieux MC Coumel P L utilisation de l amiodarone dans les troubles rythmiques graves et rebelles de l enfant Ann Cardiol Angeiol 25 385 1976

Table II Electrophysiologic results (mean ± 1 SD)

Data	Control	Immed after metoprolol	Immed after tocainide	After tocainide
Heart rate/min	66 ± 8	71 ± 13	73 ± 12	74 ± 10
A H interval (msec)	73 ± 10	81 ± 8	89 ± 12	81 ± 13
	$P < 0.02$ (Control → metoprolol)			
H V interval (msec)	37 ± 7	40 ± 6	44 ± 7	39 ± 5
Corrected sinus node recovery time at atrial pacing rate of 100/min (msec)	293 ± 222	278 ± 212	291 ± 125	3[illegible]5 ± 149
Corrected sinus node recovery time pacing rate > 100/min (msec)	157 ± 130	195 ± 65	336 ± 160	298 ± 119
			$P < 0.05$ (metoprolol → after tocainide)	
Atrial pacing rate at onset of A V Wenckebach block (beats/min)	169 ± 16	148 ± 26	143 ± 27	145 ± 28
	$P < 0.02$ (Control → metoprolol)			
Atrial effective refractory period (msec)	278 ± 63	239 ± 45	246 ± 38	247 ± [illegible]1
Atrial functional refractory period (msec)	294 ± 62	267 ± 54	27[illegible] ± 51	28[illegible] ± 51
A V nodal effective refractory period (msec)	320 ± 47	313 ± 66	321 ± 75	300 ± 34
A V nodal functional refractory period (msec)	395 ± 44	399 ± 73	399 ± 94	405 ± 26
His Purkinje effective refractory period (msec)	395 ± 44	418 ± 50	430 ± 52	405 ± 36
His Purkinje functional refractory period (msec)	401 ± 36	421 ± 40	431 ± 54	400 ± 35
			$P < 0.05$ (immed after tocainide → after tocainide)	
			$P < 0.01$ (metoprolol → after tocainide)	
Right ventricular effective refractory	236 ± 60	229 ± 34	217 ± 26	21[illegible] ± 26
Presence of ventriculoatrial (VA) conduction at right ventricular pacing rate of 100/min	4/8 = 1:1 VA conduction; 4/8 = No VA conduction	3/8 = 1:1 VA conduction; 1 = Wenckebach	3/8 = 1:1 VA conduction; 1 = Wenckebach	3 = 1:1 VA conduction; 1 = 2:1 VA block

were repeated at the end of the infusion and 15 minutes later Plasma levels of both drugs were measured at the time of hemodynamic measurements

Electrophysiologic interactions of tocainide The electrophysiologic effects of metoprolol and tocainide were assessed in eight patients (five males and three females) who were undergoing diagnostic studies for investigations of palpitations or dizziness They were premedicated with hypnotic doses of pentobarbitone All antiarrhythmic medication has been withdrawn 48 hours previously Bipolar catheters were inserted via the femoral veins into the right ventricle and also in a position to record the His bundle electrogram A quadripolar catheter was introduced via the right arm into the right atrium Another bipolar catheter was placed in the coronary sinus The intracardiac signals from these catheters were recorded together with the Frank XYZ leads Measurements of basic intracardiac conduction intervals sinus node recovery time corrected sinus node recovery time and refractory periods of the atrium A V node and right ventricle were determined by programmed stimulation Paper speed was 200 mm/sec for all studies and basic His electrogram interpretation standards were applied

Following control measurements the same basic doses and protocol design as in the hemodynamic study were used except that since the various electrical tests took longer they could be

2 Coumel P Fıdelle JE Cloup M Tournıeux MC Attuel P Tachycardıes recıproques a evolutıon prolongee chez l enfant Arch Mal Coeur 67 23 1974
3 Coumel P Fıdelle JE Attuel P Brechenmacher C et al Tachycardıes hısıenne focales congenıtales Etude cooperatıve de 7 cas. Arch Mal Coeur 69 899 1976
4 Coumel P Fıdelle JE Lucet V Attuel P Bouvraın Y Catecholamıne ınduced severe ventrıcular arrhythmıas ın children Report of four cases. Br Heart J 15(Suppl) 78 1978
5 Charlıer R Deltour G Correctıon des arythmıes experımentales par l amıodarone J Pharmacol 1 175 1970
6 Polster R Broekhuysen J The adrenergıc antagonısm of amıodarone Bıochem Pharmacol 25 131 1976
7 Sıcart M Besse P Choussat A Brıcaud H Actıon hemodynamıque de l amıodarone chez l'homme Arch Mal Coeur 70 219 1977

Table III Plasma levels of metoprolol and tocainide (mean ± 1 SD)

Metoprolol and tocainide	Haemodynamic study			
	Immed after metoprolol	*15 min after metoprolol*	*Immed after tocainide*	*15 min after tocainide*
Metoprolol (μmole/L)	0.48 ± 0.12	0.17 ± 0.05	0.[illegible]0 ± 0.0[illegible]	0.17 ± 0.0[illegible]
Tocainide (μmol/L)	0	0	83.0 ± 49.5	41.6 ± 3.9

Metoprolol and tocainide	Electrophysiologic study			
	15 min after end of metoprolol	*15 min after end of tocainide*	*30 min after end of tocainide*	*45 min after end of tocainide*
Metoprolol (μmol/L)	0.[illegible]7 ± 0.13	0.14 ± 0.05	0.13 ± 0.03	0.11 ± 0.04
Tocainide (μmol/L)	0	32.3 ± 6.6	2[illegible] ± 5.5	2[illegible]4 ± 4.9

Therapeutic ranges (1) Tocainide 18 to 80 μmol/L, and ( ) metoprolol 0.2 to [illegible]0 μmol/L (no exact therapeutic range levels are approximately those produced by 100 mg b.i.d. dose)

done once after metoprolol and twice after tocainide

Results

Hemodynamic interactions The hemodynamic findings are summarized in Table I There was a significant fall in heart rate and cardiac output following metoprolol but no additional fall after tocainide Left ventricular dP/dt max fell significantly after beta blockade and there was a further fall after tocainide Left ventricular end diastolic pressure was not altered significantly although pulmonary wedge pressure rose after tocainide but not after metoprolol Echo end diastolic dimensions were not altered after either drug There was a significant fall in mean V[illegible] and ejection fraction 15 minutes after metoprolol and again 15 minutes after tocainide

Electrophysiologic interactions The electrophysiologic results are detailed in Table II There was no change in resting heart rate The A H interval increased significantly after metoprolol but was not further affected by tocainide The H V interval was unchanged The corrected sinus node recovery time was not significantly altered during the study except that at pacing rates over 100/min there was a significant lengthening following tocainide administration The atrial pacing rate required to induce A V Wenckebach effect was significantly decreased by metoprolol but was not further altered by tocainide The refractory periods both functional and effective of the atrium A V node and right ventricle showed no significant change There was however a significant shortening of the His Purkinje system There was no consistent action on ventriculoatrial conduction (Table II)

Discussion

In our study metoprolol and tocainide singly and in combination appeared to have little influence on electrophysiologic parameters in patients who were free from sinus node disease or impaired A V conduction However when this protocol was administered to patients with underlying electrophysiologic abnormalities there was serious depression of sinus node function and A V conduction

The plasma levels of both drugs remained in the therapeutic range (Table III) There was no obvious evidence of pharmacokinetic interaction although this was not a formal pharmacokinetic study The plasma levels of both drugs immediately after infusion in the hemodynamic study were much higher than those in the electrophysiologic study This probably reflects a difference in sampling technique in that samples for the hemodynamic studies were taken from the right atrium while those for the electrophysiologic study were taken from a peripheral vein in the left arm

In conclusion the administration of tocainide and metoprolol to patients with heart disease results in a small depression of myocardial contractility This does not result in clinical sequelae Administration of the drugs especially metoprolol results in a mild depression of A V nodal conduction Tocainide shortens the functional

The clinical use of intravenous verapamil

Leo Schamroth M D *Johannesburg South Africa*

The mechanisms of action and clinical application of verapamil—a calcium ion antagonist—are reviewed Verapamil is effective and has important application in the treatment of coronary artery spasm hypertensive crises and supraventricular tachyarrhythmias

Present day pharmacologic practice usually takes the form of what might well be termed variations on a theme There are for example many variations on the penicillin theme numerous permutations on the phenothiazine theme and a thematic multiplicity of beta blocking agents Only rarely is there an event that truly constitutes a major pharmacologic breakthrough a breakthrough that reflects the development of an entirely new pharmacologic principle with dramatic clinical effects and exciting potential The introduction of calcium ion antagonists heralded by verapamil constituted such an event An event moreover that was no novel in pharmacologic action that it necessitated the addition of a fourth class to the original three class classification of antiarrhythmic substances by Singh and Vaughan Williams This new class of drugs not only inhibits the transmembrane transport of calcium ions but affects the relationship between excitation contraction coupling with profound effects on smooth muscle particularly vascular smooth muscle and on myocardial inotropism effects which have important application to clinical and especially cardiologic therapy

Basic pharmacologic action

Verapamil has three basic pharmacologic effects (1) it restricts the conversion of ATP to ADP (2) it delays or blocks conduction within the A V node and (3) it diminishes vascular and other smooth muscle tone

From th Un v rsity of th Witwatersrand nd B r gw nath Hosp tal Johannesbu g S th Africa

Repr req est Leo S hamroth M [illegible] of Med cine and Chief [illegible] Uni ers ty of W [illegible] P O Bo 2013 Johannesburg S uth Afri a

Restriction in the conversion of ATP to ADP Verapamil blocks or restricts the conversion of ATP to ADP and the consequent release of a high energy phosphate bond This results in a reduction of high energy phosphate consumption which in turn leads to a reduction in contractile tension The oxygen requirements of cardiac muscle are thereby decreased

Delay or block of conduction within the A V node A V nodal delay or block has two major therapeutic implications (1) Supraventricular impulses of atrial tachycardia atrial flutter or atrial fibrillation will be subject to increasing A V block This will reduce the ventricular response with a consequent reduction of ventricular rate (2) The circus movement of a reciprocatin supraventricular tachycardia will be interrupted within the A V node and the tachycardia thereby terminated

Diminution of vascular tone Diminution of vascular tone results in (1) coronary dilatation which thereby improves myocardial oxygen supply and (2) peripheral vasodilatation which results in a reduction in peripheral resistance with a consequent reduction in blood pressure Furthermore the reduction in peripheral resistance will also reduce the cardiac afterload and thereby the workload of the heart

Electrophysiologic effect

The plateau phase—phase 2—of the cardiac action potential is due at least in part, to a slow inward flow of calcium ions into the cell Verapamil blocks or retards this slow inward flow of calcium ions and thereby slows or prolongs both phases 2 and 3 of the cardiac action potential It has no effect on the other phases thereby indicat

0002 8703/80/131070 + 06$00 60/0 © 1980 The C V Mosby Co

refractory period of the His Purkinje system Apart from this there is little effect on conventional electrophysiologic indices in patients who are free from sinus atrial or A V nodal disease Thus they can be used with reasonable safety in these patients However, in patients with the sick sinus syndrome and impaired A V conduction significant depression of function occurs Hence their combined use in these situations is to be avoided

REFERENCES

1 Denis B Pellet J Machecourt J Martin Noel P Verapamil and beta blockade A dangerous combination Nouv Presse Med 6 2075 1977
2 Seabra Gomes R Rickards AF Sutton R Hemodynamic effects of verapamil and practolol *Eur J Cardiol 4 79* 1976
3 Boothby CB Garrard CS Pickering D Verapamil in cardiac arrhythmias Br Med J 2 349 1977
4 Gelipter D and Hazell M Interaction between disopyramide and practolol Brit Med J 1 52 1980
5 Cumming AD Robertson C Interaction between disopyramide and practolol Br Med J 2 1264 1979
6 Derrida JP Ollagnier J Benaim R Haiat R Chiche P Amiodarone and propranolol A dangerous therapeutic combination Nouv Presse Med 8 1429 1979
7 *Bigger JT Strauss HC* Digitalis toxicity Drug interactions promoting toxicity and the management of toxicity Semin Drug Treatment 2 166 1972
8 Branch RA Shand DG Wilkinson GR Nies AS The reduction of lidocaine clearance by dl propranolol An example of hemodynamic drug interaction J Pharmacol Exp Ther **184** 515 1973
9 Kessler KM Humphries WC Jr Black M Spann JF Quinidine pharmacokinetics in patients with cirrhosis or receiving propranolol AM HEART J 96 627 1978

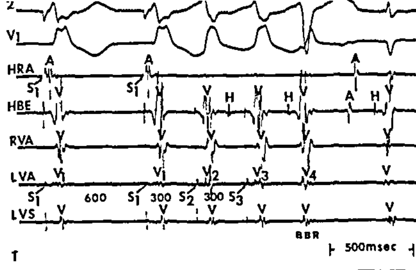


Fig 4 Bundle branch reentry following left ventricular stimulation From top to bottom are ECG Leads 2 and V and electrograms from the high right atrium *(HRA)* His bundle region *(HBE)* right ventricular apex *(RVA)* left ventricular apex *(LVA)* and left ventricular septum *(LVS)* Two ventricular extrastimuli (S S₃) are each delivered at a coupling interval of 300 msec after the eighth complex of simultaneous right atrial and left ventricular pacing (S S) at a cycle length of 600 msec S is followed by a repetitive ventricular response (V) due to achievement of marked retrograde His Purkinje conduction delay (V H) prolongation The H V interval of the extra complex (V) is 45 msec and is identical to that of the sinus complex V is similar in morphology to the paced complexes *BBR* = bundle branch reentry

usually had a configuration similar to the paced complex and was preceded by a His potential with an H V interval equal to or greater than that of a normally conducted antegrade impulse Intraventricular reentry was defined by reproducible initiation of extra ventricular complexes which were independent of V H prolongation and which occurred in the absence of His potentials or with His potentials with an H V interval less than that observed during sinus rhythm

The occurrence of sustained ventricular tachycardia was not considered diagnostic of intraventricular reentry unless patients also demonstrated in addition isolated repetitive responses

Data from the first 250 patients in this series were reviewed retrospectively and the next 150 patients were studied prospectively Results were comparable and thus were analyzed as a historical cohort Statistical significance was determined by chi square analysis

Results

Incidence of repetitive ventricular responses—relationship to organic heart disease Two hundred and thirty eight of the 400 patients (59 5%) manifested some form of repetitive ventricular response One hundred sixty (40%) had

Table I

	OHD (289 pts)	*NHD (111 pts)*
BBR	153 (108)	60 (50)
IVR	69 (24)	9 (1)
Both	45	8

BBR = bundle branch reentry IVR = intraventricular reentry OHD = organic heart disease NHD = No heart disease
Number in parentheses are the number of patients with isolated BBR and IVR

isolated bundle branch reentry 25 (6.3%) had isolated intraventricular reentry and 53 (13.3%) had both bundle branch reentry and intraventricular reentry (Fig 3 Table I) Repetitive ventricular responses were observed in 177 of 289 (61.2%) patients with organic heart disease and in 61 of 111 patients (55%) without organic heart disease ($p > 0\ 10$)

Intraventricular reentry Sixty nine of 289 (23 9%) patients with organic heart disease and nine of 111 (8 1%) patients without heart disease had intraventricular reentry ($p < 0\ 005$) Conversely of the 78 patients with intraventricular reentry 69 (88 5%) had organic heart disease while nine of 78 (11 5%) were free of demonstrable heart disease ($p < 0\ 001$) Of 58 patients with

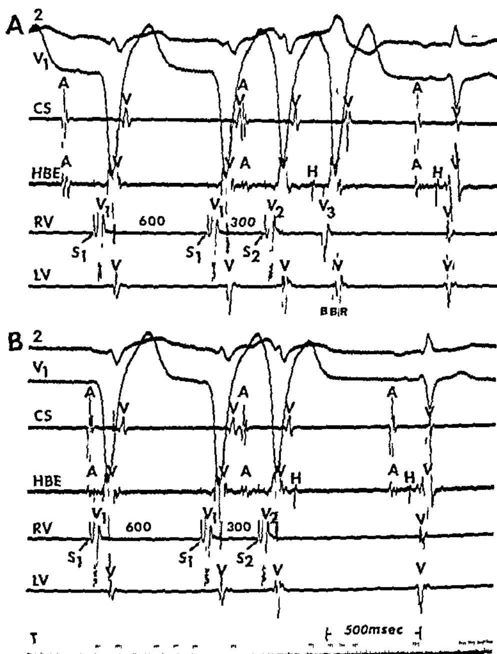


Fig 5 Abolition of bundle branch reentry by preexcitation of the His bundle The panels are organized from top to bottom as ECG Leads 2 and V *and coronary* sinus *(CS)* His bundle *(HBE)* right ventricular *(RV)* and left ventricular *(LV)* electrograms *In panel* A a premature RV stimulus *(S_2)* at a coupling interval of 300 msec results in bundle branch reentry *(BBR)* *In panel B* S is again delivered at a coupling interval of 300 msec but no BBR occurs BBR is prevented by *a spontaneous* sinus complex preceding V_2 which conducts through the A V node to pre-excite the His bundle by 70 *msec* thereby rendering it refractory to retrograde activation The supraventricular impulse blocks below the His *bundle and* no ventricular response occurs

documented ventricular tachycardia or ventricular fibrillation 43 (74%) also had repetitive ventricular responses due to *intraventricular reentry* following ventricular stimulation The *intraventricular* reentrant complexes in these patients were morphologically similar to *their* spontaneous or subsequently induced tachyarrhythmias (Fig 2) Twenty five (58%) of these 43 patients manifested isolated *intraventricular* reentry while the remaining 18 demonstrated both intraventricular reentry and bundle branch reentry However intraventricular reentry occurred in *only 9 1% (31 of 342)* of patients without malignant ventricular arrhythmias ($p < 0.001$) None

Shortcomings of the Lown grading system for observational or experimental studies in ischemic heart disease

J Thomas Bigger Jr M D and Francis M Weld M D
New York N Y

The Lown grading system uses three levels of frequency and four complex features to grade ventricular arrhythmias The seven Lown grades are mutually exclusive (a patient can be in only one grade) and hierarchical (higher grades indicate increased likelihood of death) *We evaluated the ability of the Lown arrhythmia grading system to predict death in 400 patients who were convalescing from acute myocardial infarction* Lown grading produced a poor distribution among grades of the population lacked a monotonic increase in risk with increasing arrhythmia grade lacked a substantial risk gradient between grades and showed a lack of isometry in the higher grades Also the Lown grading system thwarts the use of standard multivariate techniques for relating the frequency and characteristics of ventricular *premature depolarizations (VPDs) to cardiac death We also examined the utility of the Lown arrhythmia* equation for evaluating the results of antiarrhythmic drug therapy The Lown grading system failed to reveal clearly the change in VPD frequency and characteristics as a function of drug dose *We propose an* alternative grading system that is not mutually exclusive or hierarchical This grading system lacks many of the flaws of the Lown grading system and is suitable for standard multivariate analyses but like the *Lown grading system still fails to show the relationships among ventricular arrhythmias time drug* dose and activity

In 1971 Lown and Wolf[1] proposed a grading system for ventricular arrhythmias They contended that ventricular arrhythmias are so common in ischemic heart disease that their mere presence has little significance However these authors argued further that certain characteristics of ventricular premature depolarization (VPD) do identify persons who are prone to sudden cardiac death these characteristics are high frequency multiform VPDs repetitive VPDs and early cycle VPDs Using these VPD features they devised a system to grade ventricular arrhythmias in terms of prognostic significance The VPD grades were arranged in ascending order of gravity i e likelihood of dying In 1975 the Lown arrhythmia equation" was introduced primarily for use in experimental studies In this article we will discuss the shortcomings of the Lown system for grading ventricular arrhythmias in observational studies and in experimental studies with antiarrhythmic drugs

Use of Lown grading system in observational studies

The Lown grading system has been used to study the associations between ventricular arrhythmias and other variables or outcomes e g sudden cardiac death For example the Lown grading system has been used to investigate the relationship between ventricular arrhythmias and coronary anatomy or left ventricular dysfunction In this section we will evaluate the utility of the Lown grading system for predicting *outcome in patients who survive acute myocardial infarction* For this purpose we will use a group of 400 patients that we studied during their admission for acute myocardial infarction Each patient had a 24 hour ECG recording made 10 to 24 days after infarction These 24 hour ECG tapes were analyzed for ventricular arrhythmias by the digital computer program Columbia IV

From the Departments of Medicine and Pharmacology College of Physicians and Surgeons Columbia University New York N Y

Reprint requests J Thomas Bigger Jr M D Department of Medicine Columbia University 630 W 168th St New York NY 1003–

000?-8703/80/131081 + 08$00.80/0 © 1980 The C V Mosby Co

The automatic implantable defibrillator

M Mirowski M D Morton M Mower M D and
Philip R Reid M D *Baltimore Md*

The automatic implantable defibrillator is an electronic device programmed to monitor the cardiac rhythm continuously to recognize ventricular fibrillation and ventricular tachyarrhythmias characterized by sinusoidal waveform and to deliver corrective defibrillatory discharges when indicated Three patients suffering from recurrent malignant ventricular arrhythmias refractory to medical therapy underwent permanent implantation of this device Seven episodes of ventricular tachycardia and flutter fibrillation were documented during the weeks following the implantations two were induced at electrophysiologic studies and five occurred spontaneously All were correctly identified and six were automatically reverted to normal sinus rhythm by the implanted device one induced episode was cardioverted externally before the unit could recycle Although many problems remain to be solved and the ultimate value of this therapeutic modality has to be determined a new approach to prevention of sudden death in patients at high risk of developing lethal ventricular arrhythmias has become available

The continuing inability to deal effectively with malignant ventricular arrhythmias outside the hospital setting has prompted the development of a clinically applicable automatic implantable defibrillator[1] This device is programmed to monitor the cardiac rhythm continuously to recognize ventricular fibrillation and ventricular tachyarrhythmias characterized by sinusoidal waveforms[2] and to deliver corrective defibrillatory discharges when indicated The chief objective of the automatic defibrillator is to protect patients at particularly high risk of sudden death whenever and wherever they are stricken by these lethal arrhythmias [5] In comparison to services provided by a coronary care unit, the implanted device has the unique advantage of being permanently available to the patient at risk without interaction of specialized personnel or the need for additional equipment Conceptually the implantable defibrillator is analogous to an implantable demand pacemaker except that malignant ventricular arrhythmias instead of asystole are sensed and the delivered pulse has appropriate defibrillating characteristics

Description of the device

The first clinical model of the automatic implantable defibrillator (Fig 1) is encased in titanium and hermetically sealed with a laser weld It weighs 250 gm and occupies a volume of 145 cc All materials in contact with body tissue are biocompatible The defibrillating electrodes are made from titanium and silicone rubber One electrode designed for placement in the superior vena cava near the right atrial junction is located on the distal end of an intravascular catheter The second electrode in the form of either a cup or a flexible rectangular patch is placed extrapericardially over the apex of the heart The outside surface of the apical electrode is insulated to achieve optimal current distribution

The device is powered by lithium batteries having a projected monitoring life of approximately 3 years or a discharge capability of approximately 100 shocks The sensing system detects ventricular fibrillation by monitoring a sampled probability density function of the ven

From the Department of Medicine Sinai Hospital of Baltimore and the Cardiovascular Division of the Department of Medicine The Johns Hopkins Medical Institutions, Baltimore Md

Supported in part by Grant P 50 HL 1 655-06 from the National Heart Lung and Blood Institute National Institutes of Health and a grant from the National Aeronautics and Space Administration.

Reprint requests M Mirowski M.D Department of Medicine Sinai Hospital of Baltimore, Baltimore MD 21215

Developed and manufactured under the name of AID defibrillator by Medrad, Inc /Intec Systems, Inc Pittsburgh, P

…0/0 © 1980 The C V Mosby Co

VPD CHARACTERISTICS DETECTED BY LOWN CLASSIFICATION

Lown Grade

1 2 3 4A 4B 5

VPD < 30/hr
VPD ≥ 30/hr
MULTIFORM VPD
VPD PAIRS
VENTRICULAR TACHYCARDIA
R-on-T VPD

Fig 1 The manner in which the Lown grading hierarchy obscures VPD characteristics The Lown grades are plotted as columns of the matrix and VPD characteristics as rows The crosshatched cells indicate characteristics that are unknown in each Lown grade For example when a patient is in grade 2 all four complex features must be absent However in grade 5 there is uncertainty about VPD frequency and the presence of any complex feature except R on T

Table I The Lown grading system

Lown grade	*Definition*
0	No VPDs
1	Less than 30 VPDs/hr
2	30 or more VPDs/hr
3	Multiform VPDs
4A	Paired VPDs
4B	Ventricular tachycardia
5	R on T VPDs

Table II Comparison of three VPD frequency criteria for risk stratification in 400 patients after acute myocardial infarction

Data	*VPD frequency*		
	≥ 1/hr	*≥ 10/hr*	*≥ 30/hr*
No of patients	190	99	56
No of deaths	57	37	24
Chi square	23 1	23 4	1 5
Odds ratio	3 [illegible]	3 6	3 6
Sensitivity (%)	73	47	30
Specificity (%)	59	81	89
False positive rate (%)	71	64	60
False negative rate (%)	10	14	16

Major characteristics of the Lown grading system The Lown grading system uses three levels of frequency and four complex features to grade ventricular arrhythmias (Table I) The grades are mutually exclusive and hierarchical The system is mutually exclusive in the sense that a person can only be in one grade The system is hierarchical in two senses (1) the grade depends on the rank of the VPD features and (2) higher grades imply higher risk Each grade is assumed to have a poorer prognosis than those lower in the hierarchy

Frequency Since 1971 0 and 30 VPDs/hour have been used to partition patients into grade 0 1 or 2 It seems reasonable to select 0 VPD/hour as one of the stratifying criteria However the rationale for 30 VPDs/hour is less clear In our 400 postinfarction patients 1 0 VPD/hour is at the fiftieth percentile and 10 VPDs hour is at the seventy fifth percentile The Lown criterion for high frequency is at the eighty seventh percentile i.e only 13% of our 400 patients had 30 or more VPDs/hour Table II compares the frequency criteria of ≥ 1/hour ≥ 10 hour and ≥ 30 hour for death sensitivity specificity etc When choosing the partition value for VPD frequency the physician must consider the action to be taken in the high or low risk stratum If the low risk group is to receive treatment and follow up at a reduced level of intensity the criterion of 1/hour is best Conversely if the high risk group is to receive treatment that produces very significant undesirable effects, 30/hour is the best criterion because only about 15% of the population would be exposed to the adverse effects of treatment For many treatments the 10/hour criterion may be the best compromise between sensitivity and specificity It selects the 25% with the highest mortality rate for treatment and thus fails to expose the other 75% to the risks of treatment

It is important to remember that in the Lown grading system patients who have complex features are not classified according to VPD frequency [8] For example only 85 (30%) of the 280 patients who had a VPD frequency greater than 0/hour but less than 30/hour remained in grade 1 Similarly only 2 (4%) of the 56 patients with 30 or

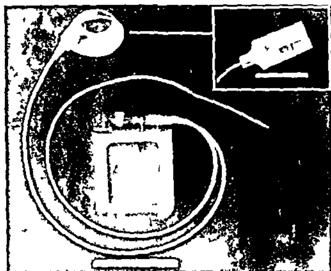


Fig 1 Automatic implantable defibrillator with its two defibrillating electrodes The insert in the upper right corner shows a patch electrode used as an alternative to the apical cup electrode

tricular electrical activity This function defines the fraction of time spent by the differentiated input electrogram between two amplitude limits located near zero potential For all practical purposes ventricular fibrillation is identified by the striking absence of isoelectric segments The device will also respond to ventricular flutter or ventricular tachycardia characterized by sinusoidal waveform if the probability density function criteria are satisfied Borderline rate and waveform characteristics of some arrhythmias may result in a delay in detection and thus in the pulse delivery The important advantages of this method of detection are its reliability low standby power requirements and most important a passive mode of failure Such a failure mode tends to ensure that possible sensing or mechanical faults will not be interpreted by the device as fibrillation and thus will not result in spurious shocks

When a suitable ventricular arrhythmia is detected the device delivers a truncated exponential pulse of 25 J 15 to 20 seconds after onset of the arrhythmia the pulse duration ranges between 3 and 8 msec as a function of the interelectrode resistance The device can recycle three times if previous discharges are ineffective, with the strength of the third and fourth pulses increased to 30 J After the fourth discharge about 35 seconds of nonfibrillating rhythm is required to reset the counter and to allow a full series of pulses to be delivered again at the next episode

Ancillary equipment

The operational readiness of the automatic defibrillator can be tested prior to and periodically following implantation [1] by an external analyzer * This noninvasive method involves triggering the capacitor charging cycle of the defibrillator with a magnet briefly placed over the skin in the area of the implanted device After becoming fully charged the capacitors are automatically discharged into a built in test load resistor rather than through the leads to the patient The analyzer measures the charging time by means of an electromagnetic transducer Progressive increase in this time normally 10 seconds or less reflects battery depletion whereas failure to initiate the cycle indicates an abnormal condition resulting in self deactivation of the device Continuous application of the magnet over the pulse generator can be used to disable the device completely and to deplete the batteries if needed

To provide information on the long term performance of the implanted defibrillator an external recorder† is available for use in selected cases This small solid state device is triggered by the defibrillatory pulse and stores 90 seconds of ECG recording 22 5 seconds preceding and 67 5 seconds following the discharge A readout console retrieves this information and indicates the number of arrhythmic episodes the total number of pulses applied when the episode occurred and the time which elapsed since the last readout

Preclinical testing

The AID defibrillator has undergone an extensive preclinical testing program to establish its effectiveness reliability and safety In addition to acute and chronic animal electrophysiologic and pathologic studies an experimental model was designed in which the clinical syndrome of sudden death from ventricular fibrillation was reproduced in active conscious dogs [1] In these animals ventricular fibrillation was induced at will by magnetically triggering an implanted alternating current generator connected to the dog s heart through a right ventricular catheter

*Developed and manufactured under the name of AIDCHECK by Medrad Inc /Intec Systems Inc Pittsburgh Pa
†Developed by The Johns Hopkins University Applied Physics Laboratory

Table III Contribution of frequency to mortality rate in patients in Lown grade 4 or 5

Lown grade	Average VPD frequency		
	≥ 10/hr	< 10/hr	Total
Grade 4A	5/18 (28%)	3/26 (12%)	8/44 (18%)
Grade 4B	7/13 (54%)	0/8 (0%)	7/21 (33%)
Grade 5	5/53 (44%)	9/63 (14%)	34/116 (29%)
Total	37/84 (44%)	12/94 (12%)	49/181 (27%)

more VPDs per hour remained in grade 2 In either high or low frequency strata the presence of complex features caused considerable movement of patients into higher Lown grades

Complex features Complex features are arranged in a hierarchy of assumed increasing risk Fig 1 lists the Lown VPD grades across the top of the graph and the VPD characteristics on the left The hatched cells represent VPD characteristics that are unknown in each Lown grade Note that if any complex VPD characteristic (grade 3 or higher) is present VPD frequency is unknown The number of unknown VPD characteristics increases as the Lown grade becomes higher so that if a patient has even one R on T VPD all frequency and other complex features are unknown There are 33 possible combinations of the three frequency levels and four complex features In our group of 400 patients 28 of the 33 possible combinations were observed The failure to observe some of the theoretically possible combinations probably results either from low prevalence of some features e g ventricular tachycardia and/or interactions among the VPD characteristics Fig 2 shows the strength of the associations among high frequency VPDs (≥ 30 VPDs/hour) and the four complex features The strongest associations were between high frequency and pairs or ventricular tachycardia and between pairs and ventricular tachycardia For example recordings with high VPD frequency are 16 7 times as likely to contain ventricular tachycardia as those with low VPD frequency

Feinstein recommends that multiple groups be combined only if each group has a similar relationship to the target outcome We tested the homogeneity among the 16 subgroups in grade 5 with respect to mortality rate Of the 116 patients in grade 5 23 (20%) had R on T as the only complex feature the mortality rate in this group was 8 7% Also in grade 5 21 patients (18%) had

STRENGTH OF ASSOCIATION (ODDS) AMONG VPD CHARACTERISTICS

	F	M	P	V	R
F		4 9	15 1*	16 7*	3 8
M			6 2	4 8	3 8
P				19 6*	4 0
V					3 6
R					

Fig 2 The associations among VPD characteristics in 400 postinfarction patients The five characteristics used in the Lown grading system are cross associated using the odds ratio a measure of strength of association F = VPD frequency of 30/hour or greater M = multiform VPD P = paired VPD V = ventricular tachycardia R = R on T VPD Since the table is symmetric only the upper half of the matrix is given Asterisks indicate the strongest associations

all four complex features the mortality rate in this group was 62% Thus subgroups with eightfold differences in mortality rates are aggregated into Lown grade 5 We conclude that interactions among VPD characteristics significantly alter prognostic significance and that aggregation of different combinations of features into higher Lown grades obscures important information about prognosis

Lown and his colleagues currently believe that VPD frequency has little prognostic significance in patients with ischemic heart disease they believe that only grades 4 and 5 predict an adverse outcome We examined the conditional probabilities of dying given the presence or absence of a VPD frequency of 10/hour or more in Lown grades 4 and 5 these data are summarized in Table III In grades 4A 4B and 5 the proportion of patients dying was significantly greater when VPD frequency was 10/hour or greater This finding demonstrates that VPD frequency does make an important contribution to the risk of dying in patients who have repetitive or R on T VPDs In grade 5 the mortality rate when neither pairs nor ventricular tachycardia are present is 10 3% in contrast the mortality rate is 48 3% when either pairs or ventricular tachycardia are present along with R on T ($P < 0.01$) Thus R on T has little prognostic significance unless associated with repetitive VPDs



Fig 2 *Left panel* Initiation of ventricular flutter fibrillation by a burst of rapid ventricular pacing *Right panel arrow* Automatic reversion of the arrhythmia to normal sinus rhythm by the implanted defibrillator I II III aVL, aVF and V are standard ECG lead *RV* = right ventricular electrogram *FAP* = femoral artery pressure

The resulting arrhythmia leads to circulatory arrest and syncope within seconds thus creating conditions for determining the long term effects and performance of the implanted device

The preclinical testing also included the analysis of long term bench performance of the implantable defibrillator and of the effects of its exposure to various physical stresses such as vacuum pressure temperature cycling mechanical vibration mechanical shock and electromagnetic interference signals Despite the fact that many of the test conditions exceeded the standards required of implanted pacemakers the results were generally satisfactory and the few detected failure modes were analyzed and corrected The AID defibrillator also underwent an independent evaluation by the Applied Physics Laboratory of The Johns Hopkins University which included basic device design provocative challenges to the sensing system and analysis of components manufacturing and quality control procedures and preclinical test results On the basis of these data the device was found suitable for use in a clinical setting

Preliminary clinical data

A pilot study of the automatic defibrillator is presently being carried out at The Johns Hopkins Hospital in patients suffering from recurrent ventricular tachyarrhythmias refractory to medical therapy [1] Specifically the candidates for implantation must have survived at least two episodes of cardiac arrest not associated with acute myocardial infarction with ventricular fibrillation documented electrocardiographically at least once One such episode must have occurred despite treatment with a medication suppressing all complex ventricular arrhythmias present or failing that despite treatment with two conventional antiarrhythmic agents given simultaneously and resulting in satisfactory blood levels Patients were excluded if they had other chronic or acute illness were on drugs other than antiarrhythmics but known to influence electrical activity of the heart or had psychological disabilities The extremely poor prognosis of patients fulfilling these criteria is exemplified by the fact that four patients identified as potential candidates for implantations of the automatic defibrillator died before they could be transferred to The Johns Hopkins Hospital

Between February and May 1980 the first three patients underwent implantation of the automatic defibrillator This group included a 57 year old woman with coronary artery disease a 16 year old boy with idiopathic cardiomyopathy and a 43 year old man with asymmetric hypertrophic cardiomyopathy All of these patients suffered from numerous episodes of ventricular fibrillation and hypotensive ventricular tachycardia requiring multiple resuscitations and external defibrillations On electrophysiologic

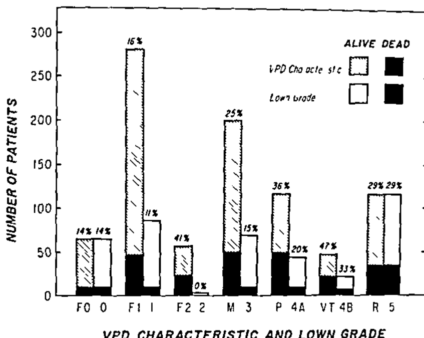


Fig 3 Comparison of VPD characteristics and Lown grades in 400 patients with ischemic heart disease Each pair of bars compares the Lown grade (right) with the characteristic that makes a person eligible for that grade *FO* = VPD frequency = 0 *F1* = VPD frequency > 0 < 30 *F2* = VPD frequency > 30 *M* = multiform VPD *P* = paired VPD *VT* = ventricular tachycardia and *R* = R on T VPD Deaths in each category are indicated by the black (lower) portion of the bars the percentages at the top of each bar represent the category specific mortality rates In grades 1 through 4B there are striking differences between the Lown grade and the characteristic that make a patient eligible for that grade

These findings serve to illustrate failings of the Lown grading system In the higher Lown grades frequency and other complex features do contribute to the risk of subsequent death The presence and intensity of these influences are hidden by the Lown grading system

Validity of the Lown grading system Feinstein has discussed criteria for judging the validity of prognostic grading systems He gives four main criteria (1) distribution of the population among the categories (2) monotonicity (3) total gradient and (4) isometry of clusters

Distribution of population When developing a grading system one hopes for a reasonably symmetric distribution among the categories with more persons in the middle than in the extreme grades Grade 2 of the Lown system presents a problem in this respect In ischemic heart disease populations less than 1% will be in grade 2 This represents a technical flaw in the Lown grading system when it is used in ischemic heart disease populations

Monotonicity If a grading system is intended to predict mortality rate then the mortality rate should increase monotonically as the grade increases If a partition (i e grade) has been ranked according to entities that do not necessarily reflect severity a monotonic trend may not occur[10] Fig 3 gives the mortality rate by Lown grade There is a notable lack of monotonicity in this grading system

Total gradient In addition to monotonicity a substantial gradient (e g 10%) between grades is desirable The Lown grading system also lacks this property There is no significant difference in the mortality rate among the first four Lown grades and there is no significant difference between the last two grades (Fig 3)

Isometry of clusters Characteristics that are combined into grades should have similar target rates As shown above subgroups with markedly different rates e g 9% to 62% are combined within grade 5 This lack of isometry will cause misclassifications that can be avoided by other grading methods In observational studies misclassification will cause confounding and mandate larger sample size and expense to detect existing relationships

Problems arising from mutually exclusive grades The mutually exclusive and hierarchical

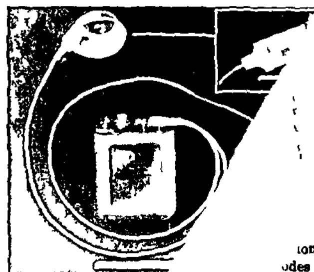


Fig 1 Automatic implant fibrillating electrodes Th shows a patch electrode cup electrode

n ion of odes of brillation two were (Fig 2) and seven were cor verted to normal ated device with a reversions were not ar irritability or asys physiologic study a ven ation, possibly provoked g unsuccessful pulse was induced ventricular tachycar ally cardioverted before the recycled In another patient a lar paced rhythm that satisfied the ensity function criteria triggered the produced no arrhythmias Although designed to treat ventricular fibrilla device has shown itself to be responsive ricular tachyarrhythmias other than ven ar fibrillation that satisfy the probability ity function criteria * a fact which broadens he spectrum of potentially correctable arrhyth mias

tricular elect the fractior input elec located purpo the s dev ve s

Significantly enough two of our initial three patients were cardioverted on a few occasions by their implanted defibrillator while awake with out feeling undue discomfort or pain Occasional ly the sensation felt was so vague that only a Holter recording confirmed the automatic rever sion of the ventricular tachycardia

These preliminary results are most encouraging and demonstrate that the automatic implantable defibrillator can successfully identify and correct malignant ventricular arrhythmias in man Although many problems remain to be solved and the ultimate value of this new therapeutic modal ity has yet to be determined a new approach has become available for the prevention of sudden death in patients who are at a particularly high risk of developing malignant ventricular arrhyth mias.

REFERENCES

1. Mirowski M Mower MM Langer A Heilman MS Schreibman J A chronically implanted system for auto matic defibrillation in active conscious dog Experimen tal model for treatment of sudden death from ventricular fibrillation Circulation 58 90 1978
2. Mirowski M Mower MM Bhagavan BS Langer A Kolenik SA Fischell RD Heilman MS Chronic animal and bench testing of the implantable automatic defibril lator *In* Meere C editor Proceedings of the Sixth World Symposium on Cardiac Pacing Tokyo 1980 chap 7 2
3. Mirowski M Reid PR Mower MM Watkins L Gott VL Schauble JF Langer A Heilman MS Kolenik SA Fischell RD Weisfeldt ML Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings N Engl J Med 303 22 1980
4. Mirowski M Mower MM Staewen WS Tabatznik B Mendeloff AI Standby automatic defibrillator An approach to prevention of sudden coronary death Arch Intern Med 126 158 1970
5. Schuder JC Stoeckle H Gold JH West JA Keskar PY Experimental ventricular defibrillation with an auto matic and completely implanted system Trans Am Soc Artif Intern Organs 16 207 1970
6. Mirowski M Mower MM Staewen WS Denniston RH Tabatznik B Mendeloff AI Ventricular defibrillation through a single intravascular catheter electrode system Clin Res 19 328 1971 (Abst)
7. Mirowski M Mower MM Staewen WS Denniston RH Mendeloff AI The development of the transvenous automatic defibrillator Arch Intern Med 129 73 1972
8. Heilman MS Langer A Mower MM Mirowski M Analysis of four implantable electrode systems for auto matic defibrillator Circulation 52(Suppl II) 194 1975 (Abst)
9. Langer A, Heilman MS Mower MM Mirowski M Considerations in the development of the automatic implantable defibrillator Med Instrum 10 163 1976
10. Schuder JC Rahmoeller GA Stoeckle H Transthoracic ventricular defibrillation with triangular and trapezoidal waveforms Circ Res 19 689 1966
11. Langer A Heilman MS Mower MM Mirowski M Functional analysis of the automatic implantable defib rillator in vivo Med Instrum 12 55 1978 (Abst)

Table IV Summary of 24 hour Holter ECG recording

Time	*Data loss (%)*	*Heart rate*	*No of VPDs*	*No of forms*	*No of pairs*	*Episodes of VT*	*Occurrences of R on T*
10 00	8 8	[illegible]	[illegible]	3	23	1	0
11 00	4 2	111	1 312	3	93	20	9
12 00	13 3	114	[illegible]	3	131	16	11
13 00	16 5	116	2 120	3	166	34	16
14 00	25 2	106	[illegible]	3	164	[illegible]	6
15 00	16 2	[illegible]	[illegible]	3	116	28	10
16 00	24 5	[illegible]	[illegible]	3	[illegible]	[illegible]	[illegible]
17 00	16 0	[illegible]	[illegible]	3	8	[illegible]	1
18 00	13 0	109	947	3	91	[illegible]	7
19 00	[illegible]	111	1 596	3	112	46	12
20 00	15 8	115	[illegible]	3	140	49	24
21 00	18 7	113	2 099	3	[illegible]	29	10
22 00	1.8	83	[illegible]	3	43	1	1
23 00	[illegible]	[illegible]	[illegible]	[illegible]	44	6	[illegible]
24 00	1 5	99	[illegible]	3	[illegible]	6	0
01 00	0 7	[illegible]	[illegible]	3	[illegible]	0	0
02 00	0 0	88	1	1	1	0	0
03 00	0 2	84	15	[illegible]	0	0	0
04 00	0.5	81	19	3	1	0	0
05 00	0 7	[illegible]	23	3	0	0	0
06 00	1 0	87	[illegible]	3	1	0	1
07 00	0 7	[illegible]	21	3	3	0	1
08 00	0 0	[illegible]	[illegible]		0	0	0
09 00	0 8	[illegible]	5	3	0	0	0
Average	8 5 ± 9 2	100 ± 12	[illegible]	3 ± 0 5	[illegible]	14 ± 16	6 ± 7

grading method used by Lown does not permit investigators to relate the frequency of VPDs to other factors (e g left ventricular function) or to relate either frequency or complex VPD features to the mortality rate Fig 3 shows the prevalence of the three VPD frequency (F) strata ($F = 0$, $0 < F < 30$ and $F \geq 30$) and the four complex features used in Lown grading these categories are not mutually exclusive Note the prevalence of frequent and complex VPD features relative to the Lown grade In Fig 3 it is easy to see that frequent VPD or repetitive VPDs (pairs and ventricular tachycardia) have a very poor prognosis Also Fig [illegible] shows how the relationship between VPD frequency or complexity and death is obscured by the Lown grading system

Alternative grading systems for observational studies In the previous discussion we have detailed a number of significant problems with the Lown grading system when it is used for observational studies in ischemic heart disease The system lacks many qualities of an excellent grading system For observational studies it is better to tabulate VPD frequency and characteristics directly (Table IV) These factors can then be related to other variables e g ischemia or ventricular function or to outcome using univariate or multivariate statistical methods Such exploration should yield improved prognostic stratification and lead to a better understanding of functional interrelationships in ischemic heart disease

Use of Lown grading system for experimental studies

A grading system for evaluating antiarrhythmic action should provide an *accurate comprehensive concise* and *understandable* summary of ventricular arrhythmias on 24 hour ECG records In this section we will examine how well the Lown grading system meets these criteria

Lown arrhythmia equation To give a more detailed view of arrhythmia response to drug action Lown et al introduced an equation that describes the arrhythmia grade in each hour of a 24 hour ECG recording Lown and Graboys[?] suggested that the equation is of special value in assessing antiarrhythmic drug efficacy The Lown equation lists the Lown arrhythmia grades on a line For each Lown grade a superscript gives

Clinical use of an implantable automatic tachycardia-terminating pacemaker

Jerry C Griffin MD Jay W Mason MD and
Richard V Calfee PhD *Stanford Calif and Freeport Tex*

A significant fraction of patients with supraventricular and ventricular tachycardia remains a therapeutic problem despite improvements in diagnostic testing new drugs and improved techniques for the evaluation of the efficacy of drug therapy Pacing provides an alternative in selected patients Pacing techniques may be used for arrhythmia suppression or termination and in rare instances may allow the substitution of a more easily managed arrhythmia We have permanently implanted a new programmable automatic tachycardia terminating pacemaker in patients with drug refractory supraventricular tachycardia Following pacemaker implantation successful tachycardia termination has been documented by ambulatory monitoring Because of changing requirements for effective termination we feel programmability is mandatory for successful long term efficacy We conclude that pacemaker therapy of supraventricular trachyarrhythmia with the automatic antitachycardia terminating pacemaker is safe effective and well tolerated

A significant number of patients with supraventricular tachyarrhythmias continues to be a therapeutic problem despite improvements in diagnostic methods new drugs and new forms of surgical therapy A number of techniques for terminating these arrhythmias utilizing pacing stimuli has been described Two types of implantable pulse generators delivering bursts of rapid atrial stimuli have been available for several years[2,3] One is adjustable but must be activated by the patient The other responds automatically to a tachycardia but is made to prescription and is not adjustable There is now available a new automatic tachycardia detecting and terminating pacemaker which is multiprogrammable allowing preimplant and noninvasive postimplant alteration of a wide range of pacemaker functions We have utilized this system for treating tachyarrhythmias in patients referred to Stanford University Medical Center

Patient selection

Patients were considered for pacemaker therapy if they were drug refractory or their tachycardia was controlled only at the expense of significant drug side effects All were adults and all were evaluated by invasive electrophysiologic study Particular emphasis was placed on the detection of extranodal pathways Patients with rapidly conducting anterograde pathways were not considered good candidates for pacing therapy because of two potential hazards (1) The induction of atrial fibrillation resulting in rapid A V conduction and (2) 1 1 A V conduction of the terminating burst In each patient consistently reliable arrhythmia termination had to be demonstrated repeatedly on more than one day

The tachycardia terminating pacemaker

The pacemaker the Cybertach 60 manufactured by Intermedics Inc is a multiprogrammable bipolar lithium powered device measuring 6 × 4 6 × 1 5 cm and weighing 95 gm It functions as a standard inhibited pacemaker with the capacity to automatically respond to tachyarrhythmias The tachycardia terminating response may be inhibited noninvasively Other programmable variables include two basic pacing rates (60 and 80 beats/min) 15 pulse durations (0 15 to 2 29 msec) and seven input sensitivity levels (0 6 to 2 8 mV) The automatic tachycardia terminating features are also programmable Twenty eight combinations of burst rate and duration are available ranging from 180 to

From the Cardiology Division Stanford University School of Medicine Stanford Calif and Intermedics Inc Freeport Tex
Reprint requests Jerry C Griffin MD Division of Cardiology Department of Medicine Stanford University School of Medicine Medical Center—S01 Stanford CA 94305

0002 8 03/80/131093 + 04$00 40 0 © 1980 The C V Mosby Co

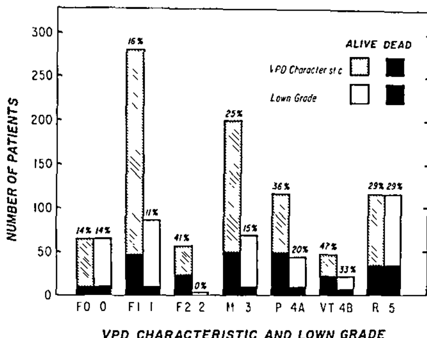


Fig 3 Comparison of VPD characteristics and Lown grades in 400 patients with ischemic heart disease Each pair of bars compares the Lown grade (right) with the characteristic that makes a person eligible for that grade *FO* = VPD frequency = 0 *F1* = VPD frequency > 0 < 30 *F2* = VPD frequency > 30 *M* = multiform VPD *P* = paired VPD *VT* = ventricular tachycardia and *R* = R on T VPD Deaths in each category are indicated by the black (lower) portion of the bars the percentages at the top of each bar represent the category specific mortality rates In grades 1 through 4B there are striking differences between the Lown grade and the characteristic that make a patient eligible for that grade

These findings serve to illustrate failings of the Lown grading system In the higher Lown grades frequency and other complex features do contribute to the risk of subsequent death The presence and intensity of these influences are hidden by the Lown grading system

Validity of the Lown grading system Feinstein[1] has discussed criteria for judging the validity of prognostic grading systems He gives four main criteria (1) distribution of the population among the categories (2) monotonicity (3) total gradient and (4) isometry of clusters

Distribution of population When developing a grading system one hopes for a reasonably symmetric distribution among the categories with more persons in the middle than in the extreme grades Grade 2 of the Lown system presents a problem in this respect In ischemic heart disease populations less than 1% will be in grade 2 This represents a technical flaw in the Lown grading system when it is used in ischemic heart disease populations

Monotonicity If a grading system is intended to predict mortality rate then the mortality rate should increase monotonically as the grade increases If a partition (i e grade) has been ranked according to entities that do not necessarily reflect severity a monotonic trend may not occur[10] Fig 3 gives the mortality rate by Lown grade There is a notable lack of monotonicity in this grading system

Total gradient In addition to monotonicity a substantial gradient (e g 10%) between grades is desirable The Lown grading system also lacks this property There is no significant difference in the mortality rate among the first four Lown grades and there is no significant difference between the last two grades (Fig 3)

Isometry of clusters Characteristics that are combined into grades should have similar target rates As shown above subgroups with markedly different rates e g 9% to 62% are combined within grade 5 This lack of isometry will cause misclassifications that can be avoided by other grading methods In observational studies misclassification will cause confounding and mandate larger sample size and expense to detect existing relationships

Problems arising from mutually exclusive grades The mutually exclusive and hierarchical

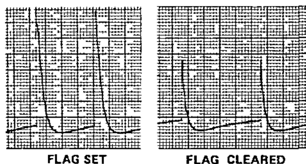


Fig 1 An electronic flag" is set in the pacemaker circuitry when a tachycardia is sensed producing the telemetry artifact seen in the left trace After reprogramming this flag is removed (small artifact)

pulses for 1 3 to 5 4 seconds The presence of an arrhythmia is determined by rate and the criteria are programmable (greater than 137 or 180 beats/min) Input signals with a frequency greater than 350/min are defined as noise no tachycardia terminating response is delivered and asynchronous pacing is initiated Application of a magnet converts the device to an asynchronous pacemaker without the tachycardia terminating response

This pacemaker also has the capacity to collect data regarding the occurrence of tachyarrhythmias to store it and to telemeter it upon command to the evaluating physician A large amplitude telemetry artifact indicates that the pacemaker has sensed a tachycardia since the last programming (Fig 1) Reprogramming or simply placing a magnet over the pacemaker clears this flag producing a small amplitude artifact The pacemaker may be interrogated directly by means of the programmer or by transtelephonic monitoring

Programmability has been important in maintaining proper pacemaker function in patients implanted with the Cybertach 60 Frequently the burst rate most effective for termination changed after the patient was ambulatory and fully recovered from the effects of hospitalization and previous drug therapy Maintenance of optimal pacing and sensing levels also necessitated adjustment of pulse duration and sensitivity level These units have been implanted by means of a transvenous tined bipolar atrial J electrode Following interpretation patients are monitored continuously and the pacemaker response to spontaneous arrhythmia is noted If adequate documentation of effective termination is not established by 72 hours the patient is returned to the electrophysiology laboratory and the arrhythmia is induced (Fig 2) Periodic 24 hour Holter monitoring is carried out in each patient to document efficient termination (Fig 3) Each patient keeps a log of the occurrence of symptoms of tachyarrhythmia If no symptoms have occurred the absence of arrhythmia is verified by interrogating the telemetry system of the pacemaker

The role of automatic pacing termination

Since the initial description by Haft et al [4] termination of supraventricular tachyarrhythmias by pacing techniques has received steadily increasing interest A variety of approaches to the management of supraventricular tachycardia by pacing techniques has been described including single random extrastimuli [7] simultaneous A V sequential pacing [9] dual demand pacing [1] orthorhythmic pacing [1] and scanning [8] In a comparison of a variety of techniques Fisher et al [3] demonstrated the greater effectiveness of bursts of rapid atrial stimulation at rates greater than 30 beats/min faster than the tachyarrhythmia Patient activated implantable devices capable of delivering bursts of rapid atrial stimuli are available and their efficacy in the chronic therapy of supraventricular tachyarrhythmias has been demonstrated [5, 6, 1, 1]

These systems do however have several shortcomings (1) They require that the patient be able to perceive both the presence and absence of tachyarrhythmia (2) They do not provide for a uniform burst duration since this is controlled by the patient (3) They require that the patient have constant access to a transmitter in the event that tachycardia should occur (4) They deliver a large amount of pacing energy to the myocardium (usually greater than 8 volts) (5) They are not effective in patients rapidly disabled by their tachyarrhythmia (6) They leave a significant residue of symptoms in patients with frequently recurring symptomatic tachycardia due to the time period necessary to perceive the arrhythmia and apply the transmitter

Custom built rapid atrial stimulators possess several advantages over radiofrequency devices in that the burst pattern is consistent in terms of energy output and burst duration In addition they provide for automatic recognition and anti

ramine (Fig 4) Fig 4 permits a comparison of th[illegible] number of hours assigned each Lown grad[illegible] (above) to the actual number of hours containin[illegible] each VPD characteristic (below) Prior to treat ment the patient has Lown grade 5 in 15 of the 2[illegible] hours recorded Lown grades 4A and 4B occur i[illegible] hours each although in reality VPD pairs [illegible] in 19 hours and ventricular tachycardia [illegible] hours There are 4 hours in Lown gra[illegible] although the patient actually has [illegible] VPDs in all but 1 hour of the 24 hour re[illegible] There are no Lown grade 2 hours howe[illegible]er [illegible] are more frequent than 30/hour during 16 [illegible] 24 hours in the pretreatment tape This di[illegible] is accounted for by the strong asso[illegible] between a VPD frequency of ≥ 30 hou[illegible] complex VPD features Because of th[illegible] tion the Lown equation provides almost no in[illegible] mation concerning VPD frequency in th[illegible] treatment record

Analysis of the response to imipramine t[illegible] (Fig 4) shows that the Lown grading syst[illegible] also inadequate for judging the efficacy of antiarrhythmic therapy Imipramine mar[illegible]edly decreases both VPD frequency and complex VPD features (Fig 4 bottom) The Lown grades (Fig 4 top) do not accurately reflect this response of VPD frequency and VPD complexity to imipra mine For example Lown grade 3 hours increase during the first day of imipramine therapy (Fig 4 top) even though there is a progressive decrease in the hours containing multiform VPDs (Fig 4 bottom) Similarly grade 2 hours show no change even though hours with frequent VPDs (≥ 30 hour) decrease markedly on the first day of imipramine treatment and then disappear entire ly Thus the Lown grading system may provide only limited insight into the magnitude or even the direction of the response of individual VPD characteristics to antiarrhythmic therapy

We contend that a few simple modifications of the Lown arrhythmia equation provide a much more valuable tool for evaluating the response of ventricular arrhythmias to therapy We recom mend the following changes (1) count the actual VPD characteristics rather than Lown grades (2) count each complex VPD feature independent of VPD frequency or any other complex VPD features and (3) use subscripts for VPD charac teristics that apply to *all* hours of the ECG recording We replace Lown grades 0 1 and 2 with a single frequency category F The first superscript (prehyphen) for F is the number of

[illegible] cord [illegible] of data [illegible] d The [illegible] fre[illegible] d for [illegible] in all [illegible] Lown grad[illegible] 4A [illegible] for [illegible] for VPD [illegible] ventricul[illegible]r [illegible] P for [illegible] VPD [illegible] count [illegible] the VPD characteristic occu[illegible] to M is the number of different VPD configurations on the entire ECG recording and the subscripts to P V and R refer to the total number of the e events in the ECG record [illegible] use a econd subscript to R to give the shor[illegible] R V/Q T interval in the ECG recording

To compare our notation to the Lown arrhyth mia equation we compared the three ECG records in Fig 4

Lown arrythmia equation

Pretreatment	0	1	2^0_0	3^4_3	$4A_7$	$4B_{6\text{-}3}$	5^{15}_{21}
Treatment No 1	0	1	2^0_0	3^{19}_3	$4A^0_0$	$4B^0_0$	5^0_0
Treatment No 2	0	1	2^0_0	3^7_2	$4A^0_0$	$4B^0_0$	5^0_0

Modified arrhythmia equation

Pretreatment	$F^{24\text{-}1}_{16.0}$	M^{23}_3	P^{19}_{1964}	$V^{15}_{344\text{-}6}$	$R^{15}_{131\text{-}0.59}$
Treatment No 1	$F^{20\text{-}0.4}_{13.3}$	M^{19}_3	P^0_0	V^0_0	R^0_0
Treatment No 2	$F^{20\text{-}3}_{4.3}$	M^7_2	P^0_0	V^0_0	R^0_0

The subscript of the F category (average VPDs per hour) in our notation accurately shows the pronounced drop in VPD frequency during imip ramine therapy whereas the Lown equation does not Our notation permits rapid calculation of the *total* number of VPDs (F superscript multiplied by F subscript) The Lown arrhythmia equation *does* not permit calculation of average VPD frequency or of total VPDs in an ECG recording *Our* notation reveals the progressive decrease in multiform VPDs during treatment Lown grade 3 does not reveal this response Also our notation clearly enumerates the repetitive activity in the ECG recordings whereas Lown grades 4A and 4B do not For these rea ons, we feel that the modi

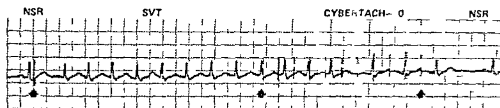


Fig 2 Illustrating the function of the tachycardia terminating pacemaker On the left hand portion of the continuous ECG strip the rhythm is sinus A single premature extrastimulus is placed during the relative refractory period of the A V node inducing supraventricular tachycardia After counting eight consecutive intervals shorter than the programmed tachycardia criteria the pacemaker responds with a burst of rapid stimuli that terminate the arrhythmia restoring normal sinus rhythm

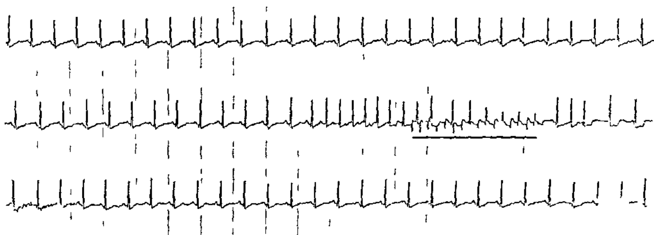


Fig 3 Tracing taken from a 24 hour Holter monitor study illustrates the termination of a spontaneous episode of supraventricular tachycardia The upper tracing shows 20 seconds of normal sinus rhythm The middle tracing shows normal sinus rhythm followed by ? beats of supraventricular tachycardia The tachycardia terminating pacemaker is then activated for 4 seconds ?40 pulses/min after which sinus rhythm is restored

tachycardia response freeing the patient from the problems of keeping a transmitter available and applying it after the onset of symptoms However these units possess significant disadvantages when compared to the programmable automatic burst pacemaker There is a significant delay once the decision for pacing therapy is made to have a device adjusted and furnished to the implanting physician Most important this type of unit does not allow subsequent flexibility to respond to changes in pacemaker requirements We have found significant changes in the requirements for optimal burst termination between the artificial setting of the catheterization laboratory and the chronic circumstance of an ambulatory patient with a chronically implanted electrode

The atrial stimulator used in our patients is extensively programmable and fully automatic It responds with a burst of stimuli at a uniform rate and duration after sensing eight consecutive RR intervals sufficiently brief in duration to meet the program criteria for the definition of tachycardia For a tachycardia of 150 beats/min less than 6 seconds is usually required for sensing and termination Therefore patients are usually only transiently aware if at all of the presence and termination of tachycardia

Due to the extensive programmability follow up evaluation of these patients can be quite complete At each clinic visit thresholds for pacing and sensing in normal sinus rhythm are determined In certain patients with easily inducible arrhythmias pacemaker efficacy can be tested by the application of a magnet This produces single random extrastimuli which eventually will initiate an episode of tachycardia

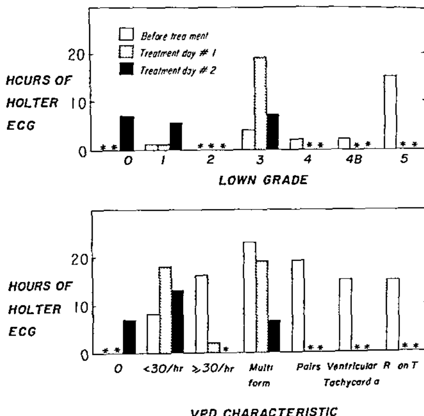


Fig 4 The use of the Lown grading system to summarize the results of an antiarrhythmic drug trial with imipramine Above the Lown system is used to summarize the findings in three 24 hour Holter ECG recordings tape 1 = pretreatment tape 2 = lower dose and tape 3 = higher dose Below the same three tapes have been summarized by tabulating all hours containing the VPD characteristic only the frequency characteristics are mutually exclusive An asterisk indicates that the Lown grade or the VPD characteristic was not present in any hour of the recording The Lown grades do not accurately reflect the hourly count for VPD characteristics (see below) and do not accurately reflect the response of VPD characteristics to therapy

the number of hours in the 24 hour ECG recording which is assigned to that grade Subscripts further characterize some Lown grades for grade 2 the subscript gives the number of VPDs in the grade 2 hours for grade 3 the subscript denotes the maximum number of VPD configurations observed in any single grade 3 hour for grade 4A the subscript gives the maximum number of VPD pairs in any grade 4 hour for grade 4B the first subscript refers to the maximum number of episodes of ventricular tachycardia in a single grade 4B hour while the second subscript indicates the number of cycles in the longest run of ventricular tachycardia for grade 5 the subscript identifies the maximum number of R on T VPDs occurring in any grade 5 hour

The Lown equation has several ambiguities and drawbacks First no account is given of the noise that frequently occurs in ambulatory ECG recordings Noise reduces the VPD count and if an adjustment is not made the calculated VPD frequency will be too low Noise also increases the likelihood of false positive VPDs Both of these effects make noise important to report Second the equation makes it difficult to determine VPD frequency or other VPD characteristics In the Lown grades a subscript applies only to the hours assigned to its grade [13] Thus if five VPD configurations exist in a 24 hour ECG recording but only two appear in any grade 3 hour the subscript for grade 3 will be 2 not 5 Similarly the subscript to grade 2 does not count the VPDs occurring in higher grades This convention makes it impossible to calculate VPD ency d for a 24 hour ECG recording Third is given for grade 1 therefore th VPDs in Lown grade 1 hours

To illustrate the use of intervention trials we and individual VPD ch ambulatory ECG record undergoing anti

Pacing and sensing thresholds can then be deter mined during tachycardia Several burst patterns can be tested and the most effective one deter mined

We feel pacing has significant advantages when compared with pharmacologic therapy With antiarrhythmic drugs adverse effects are com mon frequently resulting in significant morbidity and occasional death The patient is freed from the nuisance of taking multiple doses of medica tion each day Pacing may be an especially effec tive form of therapy for those patients who are unreliable Pacing for supraventricular arrhyth mias of course carries some complications as well It requires a surgical procedure for implan tation and carries with it all the usual complica tions of pacemaker implantation In addition patients treated in this way are at risk of the induction of atrial fibrillation which if persistent may require cardioversion

This pacemaker provides safe and effective therapy for supraventricular tachyarrhythmias It is most applicable in those patients unrespon sive to pharmacologic therapy unaware of the presence of supraventricular arrhythmias and/or rapidly disabled by their tachycardias Tachycar dia therapy with the automatic tachycardia terminating pacemaker has a high level of patient acceptance due to the freedom from the expense side effects and nuisance of drug therapy

REFERENCES

1 Curry PVL Rowland E Krikler DM Dual demand pacing for refractory atrioventricular reentry tachycar dia PACE 2 137 1979

2 Fisher JD Furman S Duffin EG Automatic implanted rapid burst pacer for refractory ventricular tachycardia Clin Res 27 164 A 1979

3 Fisher JD Ostrow E Rosenberg P Kim SG Atrial vulnerability to electrophysiologic stresses Clinical cor relations In Proceedings of the Sixth World Symposium on Cardiac Pacing Tokyo 1979 chap 9 16

4 Haft JI Kosowsky BD Lau SH Stein E Damato AN Termination of atrial flutter by rapid electrical pacing of the atrium Am J Cardiol 20 239 1967

5 Kahn A Morris JJ Citron P Patient initiated rapid atrial pacing to manage supraventricular tachycardia Am J Cardiol 38 200 1976

6 Peters RW Shafton E Frank S Thomas AN Scheinman MM Radio frequency triggered pacemakers Use and limitations Ann Intern Med 88 17 1978

7 Ryan GF Easley RM Zaroff LI Goldstein S Paradoxi cal use of a demand pacemaker in treatment of supraven tricular tachycardia due to the Wolff Parkinson White syndrome Circulation 38 1037 1968

8 Spurrell RAJ Sowton E The management of paroxys mal supraventricular tachycardia using a scanning pace maker system Cardiac pacing In Proceedings of the Sixth International Symposium on cardiac pacing 19 [illegible] Tokyo p 212

9 Sung RJ Styperek JL Castellanos A Complete aboli tion of the reentrant supraventricular tachycardia zone using a new modality of cardiac pacing with simulta neous atrioventricular stimulation Am J Cardiol 45 [illegible] 1079

10 Todo K Kaneko S Fujiwara T Sugiki K Tanaka N Komatsu S Patient controlled rapid atrial pacing in the long term management of recurrent supraventricular tachycardias In Proceedings of the Sixth World Sympo sium on cardiac pacing Tokyo 1979 chap 9 16

11 Waxman MB Wald RW Bonnet JF MacGregor DC Goldman BS Self-conversion of supraventricular tachy cardia by rapid atrial pacing PACF 1 [illegible] 1978

12 Zacouto FI Guize LJ Fundamentals of orthorhythmic pacing In Luderitz B editor Cardiac pacing Berlin 1976 Springer Verlag p 212

ramine (Fig 4) Fig 4 permits a comparison of the number of hours assigned each Lown grade (above) to the actual number of hours containing each VPD characteristic (below) Prior to treatment the patient has Lown grade 5 in 15 of the 24 hours recorded Lown grades 4A and 4B occur in 2 hours each although in reality VPD pairs occur in 19 hours and ventricular tachycardia in 15 hours There are 4 hours in Lown grade 3 although the patient actually has multiform VPDs in all but 1 hour of the 24 hour record There are no Lown grade 2 hours however VPDs are more frequent than 30/hour during 16 of the 24 hours in the pretreatment tape This disparity is accounted for bv the strong association between a VPD frequency of ≥ 30/hour and complex VPD features Because of this association the Lown equation provides almost no information concerning VPD frequency in the pretreatment record

Analysis of the response to imipramine therapy (Fig 4) shows that the Lown grading system is also inadequate for judging the efficacy of antiarrhythmic therapy Imipramine markedly decreases both VPD frequency and complex VPD features (Fig 4 bottom) The Lown grades (Fig 4 top) do not accurately reflect this response of VPD frequency and VPD complexity to imipramine For example Lown grade 3 hours increase during the first day of imipramine therapy (Fig 4 top) even though there is a progressive decrease in the hours containing multiform VPDs (Fig 4 bottom) Similarly grade 2 hours show no change even though hours with frequent VPDs (≥ 30/hour) decrease markedly on the first day of imipramine treatment and then disappear entirely Thus the Lown grading system may provide only limited insight into the magnitude or even the direction of the response of individual VPD characteristics to antiarrhythmic therapy

We contend that a few simple modifications of the Lown arrhythmia equation provide a much more valuable tool for evaluating the response of ventricular arrhythmias to therapy We recommend the following changes (1) count the actual VPD characteristics rather than Lown grades (2) count each complex VPD feature independent of VPD frequency or any other complex VPD features and (3) use subscripts for VPD characteristics that apply to *all* hours of the ECG recording We replace Lown grades 0 1 and 2 with a single frequency category F The first superscript (prehyphen) for F is the number of consecutive hours of ECG analyzed the second (posthyphen) superscript shows the hours of data loss due to noise in the hours analyzed The subscript for F is the average hourly VPD frequency for all hours analyzed (adjusted for noise) This new notation (1) clearly indicates 24 hour average VPD frequency (2) avoids dichotomizing at an arbitrary frequency value (3) condenses all frequency information into a single category and (4) accounts for data loss due to noise Accounting for data loss permits the investigator to correct the observed counts in all categories We have replaced Lown grades 3 4A 4B and 5 with M P V and R respectively M for multiform P for VPD pairs V for ventricular tachycardia and R for R on T VPD In our notation superscripts represent a count of *all* hours in which the VPD characteristic occurs The subscript to M is the number of different VPD configurations on the entire ECG recording and the subscripts to P V and R refer to the total number of these events in the ECG record We use a second subscript to R to give the shortest R V/Q T interval in the ECG recording

To compare our notation to the Lown arrhythmia equation we compared the three ECG record in Fig 4

Lown arrythmia equation

Pretreatment	0'	1	2^{0}_{0}	3^{4}_{3}	$4A^{2}_{7}$	$4B^{2}_{6\text{-}3}$	5^{15}_{24}
Treatment No 1	0'	1	2^{0}_{0}	3^{19}_{3}	$4A^{0}_{0}$	$4B^{0}_{0}$	5^{0}_{0}
Treatment No 2	0	1	2^{0}_{0}	3^{7}_{2}	$4A^{0}_{0}$	$4B^{0}_{0}$	5^{0}_{0}

Modified arrhythmia equation

Pretreatment	$F^{24\text{-}2\,1}_{916\,0}$	M^{23}_{3}	P^{19}_{1864}	$V^{15}_{344\text{-}6}$	$R^{15}_{131\text{-}029}$
Treatment No 1	$F^{20\text{-}0\,4}_{13\,3}$	M^{19}_{3}	P^{0}_{0}	V^{0}_{0}	R^{0}_{0}
Treatment No 2	$F^{20\text{-}2\,3}_{4\,3}$	M^{7}_{2}	P^{0}_{0}	V^{0}_{0}	R^{0}_{0}

The subscript of the F category (average VPDs per hour) in our notation accurately shows the pronounced drop in VPD frequency during imipramine therapy whereas the Lown equation does not Our notation permits rapid calculation of the total number of VPDs (F superscript multiplied by F subscript) The Lown arrhythmia equation does not permit calculation of average VPD frequency or of total VPDs in an ECG recording Our notation reveals the progressive decrease in multiform VPDs during treatment Lown grade 3 does not reveal this response Also our notation clearly enumerates the repetitive activity in the ECG recordings whereas Lown grades 4A and 4B do not For these reasons we feel that the modi

[illegible] equation is a better tool for [illegible] than the Lown grading sys[illegible] for antiarrhythmic drug trials [illegible] and understandable as [illegible] but it is more comprehensive [illegible]

[illegible] shortcomings of the Lown grad[illegible] for experimental studies [illegible] Lown grading it is not possible to relate [illegible] to drug dosing time of day or [illegible] all of which can importantly modify [illegible] arrhythmias.[14] Neither the Lown [illegible] arrhythmia equation nor our notation permits a [illegible] relationships In Table IV we show [illegible] hour-by hour occurrence of ventricular arrhythmias for the pretreatment ECG shown in Fig 4 and in the pretreatment arrhythmia equations There is an obvious decrease in VPD frequency and complex VPD forms during sleep which cannot be appreciated when the data are displayed without the dimension of time The timing of ventricular arrhythmias (Table IV) especially the relationship of ventricular arrhythmias to times of peak and trough serum drug levels can be crucial in determining a successful antiarrhythmic drug dose and dosing interval.[11, 15] If significant ectopy persists in a 24 hour ECG recording *after* initiation of antiarrhythmic drug therapy the relationship of the residual ectopy to drug dose to dosing interval, and to activity [illegible]d be carefully evaluated For this purpose [illegible] tabulations that include the dimension [illegible] time (such as Table IV) are superior to the exposition of data in an arrhythmia equation

REFERENCES

1. Lown B Wolf M Approaches to sudden death from coronary heart disease Circulation 44 130 1971
2. Lown B Calvert AF Armington R Ryan M Monitoring for serious arrhythmias and high risk of sudden death Circulation 52 III 189 1975
3. Calvert A Lown B Gorlin R Ventricular premature beats and anatomically defined coronary heart disease Am J Cardiol 39 627 1977
4. Schulze RA Humphries JO Griffith LSC Ducci H Achuff S Baird M Mellits E Pitt B Left ventricular and coronary angiographic anatomy Relationship to ventricular irritability in the late hospital phase of acute myocardial infarction Circulation 55 839 1977
5. Schulze RA Jr Strauss HW Pitt B Sudden death in the year following myocardial infarction Relation to ventricular premature contractions in the late hospital phase and left ventricular ejection fraction Am J Med 62 192 1977
6. Birman KP Rolnitzky LM Bigger JT Jr A shape oriented system for automated Holter ECG analysis *In* Computers in cardiology Long Beach Calif 1978 IEEE Computer Society p 217
7. Bigger JT Jr New directions and new uses for risk stratification in the post hospital phase of acute myocardial infarction Am J Med 67 1 1979
8. Bigger JT Jr Wenger TL Heissenbuttel RH Limitations of the Lown grading system for the study of human ventricular arrhythmias AM HEART J 93 727 1977
9. Fleiss JL Statistical methods for rates and proportions. New York, 1973 John Wiley & Sons, Inc
10. Feinstein AR Clinical biostatistics St Louis 1977 The C V Mosby Co
11. Lown B Graboys TB Management of patients with malignant ventricular arrhythmias Am J Cardiol 39 910 1977
12. Lown B Sudden cardiac death The major challenge confronting contemporary cardiology Am J Cardiol 43 313 1979
13. Lown B Cardiovascular collapse and sudden cardiac death *In* Braunwald E editor Heart disease A textbook of cardiovascular medicine Philadelphia 1980 W B Saunders Co
14. Lown B Verner RL Rabinowitz SH Neural and psychologic mechanisms and the problem of sudden cardiac death Am J Cardiol 39 890 1977
15. Winkle RA Alderman EL Fitzgerald JW Harrison DC Treatment of recurrent symptomatic ventricular tachycardia Ann Intern Med 85 1 1976

Pacing and sensing thresholds can then be determined during tachycardia Several burst patterns can be tested and the most effective one determined

We feel pacing has significant advantages when compared with pharmacologic therapy With antiarrhythmic drugs adverse effects are common frequently resulting in significant morbidity and occasional death The patient is freed from the nuisance of taking multiple doses of medication each day Pacing may be an especially effective form of therapy for those patients who are unreliable Pacing for supraventricular arrhythmias of course carries some complications as well It requires a surgical procedure for implantation and carries with it all the usual complications of pacemaker implantation In addition patients treated in this way are at risk of the induction of atrial fibrillation which if persistent may require cardioversion

This pacemaker provides safe and effective therapy for supraventricular tachyarrhythmias It is most applicable in those patients unresponsive to pharmacologic therapy unaware of the presence of supraventricular arrhythmias and/or rapidly disabled by their tachycardias Tachycardia therapy with the automatic tachycardia terminating pacemaker has a high level of patient acceptance due to the freedom from the expense side effects and nuisance of drug therapy

REFERENCES

1 Curry PVL Rowland E Krikler DM Dual demand pacing for refractory atrioventricular reentry tachycardia. PACE 2 137 1979

2. Fisher JD Furman S Duffin EG Automatic implanted rapid burst pacer for refractory ventricular tachycardia Clin Res 27 164 A 1979

3 Fisher JD Ostrow E Rosenberg P Kim SG Atrial vulnerability to electrophysiologic stresses Clinical correlations *In* Proceedings of the Sixth World Symposium on Cardiac Pacing Tokyo 1979 chap 9 16

4 Haft JI Kosowsky BD Lau SH Stein E Damato AN Termination of atrial flutter by rapid electrical pacing of the atrium Am J Cardiol 20 239 1967

5 Kahn A Morris JJ Citron P Patient initiated rapid atrial pacing to manage supraventricular tachycardia Am J Cardiol 38 200 1976

6 Peters RW Shafton E Frank S Thomas AN Scheinman MM Radio frequency triggered pacemakers Use and limitations Ann Intern Med 88 17 1978

7 Ryan GF Easley RM Zaroff LI Goldstein S Paradoxical use of a demand pacemaker in treatment of supraventricular tachycardia due to the Wolff Parkinson White syndrome Circulation 38 1037 1968

8 Spurrell RAJ Sowton E The management of paroxysmal supraventricular tachycardia using a scanning pacemaker system Cardiac pacing *In* Proceedings of the Sixth International Symposium on cardiac pacing 1976 Tokyo p 212

9 Sung RJ Styperek JL Castellanos A Complete abolition of the reentrant supraventricular tachycardia zone using a new modality of cardiac pacing with simultaneous atrioventricular stimulation. Am J Cardiol 45 ?? 1079

10 Todo K Kaneko S Fujiwara T Sugiki K Tanaka N Komatsu S Patient controlled rapid atrial pacing in the long term management of recurrent supraventricular tachycardias *In* Proceedings of the Sixth World Symposium on cardiac pacing Tokyo 1979 chap 9-16

11 Waxman MB Wald RW Bonnet JF MacGregor DC Goldman BS Self conversion of supraventricular tachycardia by rapid atrial pacing PACE 1 35 1978

12 Zacouto FI Guize LJ Fundamentals of orthorhythmic pacing *In* Luderitz B editor Cardiac pacing Berlin 1976 Springer Verlag p 212

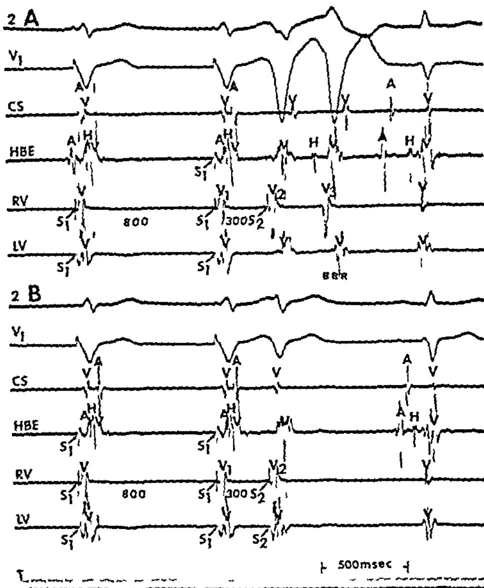


Fig. 6. Prevention of bundle branch reentry by simultaneous right and left ventricular stimulation. The figure is organized as *Fig. 4*. In *panel A*, a right ventricular premature stimulus (S_2) is delivered at a coupling interval of 300 msec during ventricular pacing (S_1-S_1) at a cycle length of 800 msec, resulting in bundle branch reentry (*BBR*) as previously described. In *panel B* simultaneous right and left ventricular stimulation at the same coupling intervals as in panel A failed to induce BBR. Simultaneous stimulation of the opposite ventricle renders the retrograde limb of the BBR pathway (LV conduction system) refractory, thereby abolishing reentry.

of the patients with documented ventricular tachycardia/fibrillation had only bundle branch reentry.

Characteristics of repetitive ventricular responses. Bundle branch reentry usually had a configuration similar to the ventricular paced complex that initiated this response at longer coupling intervals (i.e., right bundle branch block pattern for left ventricular premature stimuli and left bundle branch pattern for right ventricular premature stimuli) (Figs. 1 and 4). However, changes in morphology were observed at very close coupling intervals. Regardless of the ventricle of stimulation, bundle branch reentry occurred only when a critical degree of V-H delay was attained. The range of retrograde His-Purkinje conduction delay (V-H interval) required for initiation was 160 to 300 msec. In most

Table II

	VT/VF (58 pts)	RBBB (35 pts)	LBBB (17 pts)
BBR	29	2	1
IVR	43	20	8
None	8	14	8

BBB = bundle branch block R = right L = left BBR = bundle branch reentry IVR = intraventricular reentry VT/VF = ventricular tachycardia/ventricular fibrillation

patients demonstrating bundle branch reentry this response was elicited with a single premature ventricular stimulus during ventricular pacing in 11 patients (5%) double premature ventricular stimuli were required

The degree of retrograde His Purkinje conduction delay produced during ventricular stimulation was the same in patients who developed bundle branch reentry as in those who failed to develop this phenomenon The presence or absence of organic heart disease was not related to the appearance of retrograde conduction delay However retrograde conduction delay was only noted in 12 of the 35 (34 3%) patients with right bundle branch block and was observed in 296 patients (85%) without conduction delay

There was a direct relationship between paced cycle length and the coupling interval of bundle branch reentrant complexes This was related to a longer His Purkinje refractory period at the longer paced cycle length therefore facilitating the development of retrograde His Purkinje delay in response to ventricular extrastimuli No bundle branch reentry was observed during retrograde gap phenomena In addition bundle branch reentry did not occur when spontaneous or stimulated supraventricular complexes pre excited the His bundle antegradely prior to the time it would have been engaged retrogradely during ventricular extrastimuli (Fig 5) or when ventricular extrastimuli were delivered simultaneously in both ventricles (Fig 6) Bundle branch reentry produced one to four extra complexes but was never sustained

In contradistinction to responses due to bundle branch reentry intraventricular reentrant complexes appearing after single (63 patients 81%) or only after double ventricular extrastimuli (15 patients 19%) frequently had a configuration distinctly different from that of the paced ventricular complex Intraventricular reentry occurred in the absence of definite retrograde H potentials in approximately 80% of patients with these responses, and with H V intervals shorter than those in sinus rhythm in the remainder (16 patients) Intraventricular reentry most often occurred during stimulation within 25 msec of the ventricular refractory period however in 20 patients with ventricular tachycardia or ventricular fibrillation there was a zone of at least 50 msec prior to ventricular refractoriness when the intraventricular reentrant complexes were noted. In patients who subsequently developed sustained ventricular tachycardia the intraventricular reentrant complex resembled the configuration of the complexes during ventricular tachycardia regardless of the site of stimulation (Fig 2) In three patients ventricular tachycardia was only inducible with programmed electrical stimulation of the left ventricle In these three patients intraventricular reentrant complexes were only elicited with left ventricular stimulation and occurred with right bundle branch block morphologies Supraventricular stimuli did not prevent intraventricular reentry nor did biventricular stimulation prevent it in ten patients in whom these perturbations were attempted

In patients who demonstrated both bundle branch reentry and intraventricular reentry the zones of coupling intervals which produced each were different although some overlap appeared In ten cases bundle branch reentrant complexes acted as a secondary ventricular premature extrastimulus inducing intraventricular reentry When this was observed the bundle branch reentry occurred at coupling intervals similar to those found capable of inducing intraventricular reentry with double premature ventricular extrastimuli In seven patients intraventricular reentry was associated with the appearance of unrelated retrograde His potentials

Of the 19 patients who had ventricular fibrillation prior to study four had no demonstrable organic cardiac disease, only one of these four had intraventricular reentry and this patient was the only one of the four with inducible ventricular fibrillation Of the 15 patients with heart disease and ventricular fibrillation 11 had intraventricular reentrant complexes eight of these 11 had inducible ventricular fibrillation In each case these intraventricular reentrant complexes were

branch block morphology rarely developed bundle branch reentry[1,4] This appears to reflect prolonged retrograde as well as antegrade conduction and refractoriness[1,4,7] However, a higher than expected percentage of patients with bundle branch block developed intraventricular reentry (55% versus 19%) Therefore not surprisingly, a high incidence of ventricular arrhythmias has been reported in patients with such conduction disturbances, and ventricular fibrillation rather than heart block has been suggested as the cause of sudden death in many of these patients[8,9] These relationships provide further support that intraventricular reentry is a marker for those patients prone to develop malignant ventricular tachyarrhythmias

In conclusion two different mechanisms of repetitive ventricular responses encountered during ventricular stimulation exist One bundle branch reentry involves a macroreentrant circuit involving the bundle branches and is a benign phenomenon occurring in more than half the patients in whom ventricular stimulation is carried out Intraventricular reentry on the other hand represents a pathological event closely related to clinical ventricular arrhythmias

Summary

Repetitive ventricular responses (RVR) to programmed ventricular stimulation were observed in 238 of 400 patients (59 5%) Two types of RVR with different mechanisms and clinical significance in relation to ventricular arrhythmias could be identified

1 Repetitive ventricular responses resulting from bundle branch reentry occurred in 53% of patients without any significant difference of incidence in the presence (52 9%) or absence (54 1%) of organic heart disease

2 Repetitive ventricular responses resulting from intraventricular reentry occurred in 19 5% of patients with a significantly higher incidence in patients with (23 9%) than without (8 1%) organic heart disease Thirty eight of 41 (92 7%) patients with inducible ventricular tachycardia or fibrillation also had intraventricular reentry but only 9 1% of patients without these arrhythmias manifested intraventricular reentry ($p < 0\ 005$) Moreover the mode of induction and the configuration of intraventricular reentry was closely related to that of ventricular tachycardia when induced

It is concluded that bundle branch and intraventricular reentry are different phenomena both in mechanism and relationship, to spontaneous ventricular arrhythmias Bundle branch reentry appears to be a benign phenomenon which represents a physiological response of the His Purkinje system and is not directly related to ventricular arrhythmias On the other hand our data suggest that intraventricular reentry may be a 'pathologic phenomenon closely related to ventricular arrhythmias The presence of intraventricular reentry may identify patients who are prone to develop ventricular tachycardia or fibrillation

The authors gratefully acknowledge the help of Marie Coscia and Charlotte Drzewiecki for their secretarial assistance Blance Douglas Karen Resko and Margaret Rokus are thanked for their technical assistance and we are especially grateful to John A Kastor M D Chief of the Cardiovascular Section Hospital of the University of Pennsylvania for his continued support and encouragement

REFERENCES

1 Akhtar M Damato A N Batsford W P Ruskin J N Ogunkelu J B and Vargas G Demonstration of reentry within the His Purkinje system in man Circulation 50 1150 1974

2 Drew T M Josephson M E Horowitz L N Kastor J A and Herling I The significance of the repetitive ventricular response to programmed ventricular stimulation (Abstr) Clin Res 25 218A 1977

3 Schuilenburg R M Patterns of V A conduction in the human heart in the presence of normal and abnormal A V conduction *in* The conduction system of the heart Wellens H J J Lie K I and Janse M J editors, Philadelphia 1976 Lea & Febiger chapt 27 pp 485 503

4 Akhtar M and Damato A N Intraventricular reentry in patients with pre existing right/left bundle branch block (Abstr) Circulation 56 III 107 1977

5 Wellens H J J Durer D R and Lie K I Observations on mechanisms of ventricular tachycardia in man Circulation 54 237 1976

6 Josephson M E Horowitz L N Farshidi A and Kastor J A Recurrent sustained ventricular tachycardia 1 Mechanisms Circulation 57 431 1978

7 Josephson M E and Kastor J A Retrograde His Purkinje conduction during retrograde stress J Clin Invest 61 171 1978

8 Watanabe Y Pamintuan J C and Dreifus L S Role of intraventricular con[illegible] on d[illegible] turbances in ventricular premature systoles [illegible] [illegible]nl 32 188 1973

9 W[illegible]

multiple (≥ three complexes) and were often polymorphic, resembling so-called *torsade de pointe*.

Of the 39 patients who had sustained ventricular tachycardia, nine had no organic cardiac lesion; only four of these nine patients had inducible ventricular tachycardia and three of these four had intraventricular reentries. Of the 30 patients with known cardiac disease, 28 had inducible ventricular tachycardia and 26 of these 28 had intraventricular reentries. Intraventricular reentry did not necessarily occur at the same drive cycle length (S_1S_1) that was utilized during induction of ventricular tachycardia, and reentrant complexes occurred with single extrastimuli in five patients who required double ventricular extrastimuli for initiation of ventricular tachycardia. Two patients with noninducible ventricular tachycardia also had intraventricular reentry. Conversely, of 78 patients demonstrating intraventricular reentry, 43 had documented spontaneously occurring sustained ventricular tachycardia or ventricular fibrillation; 38 of these 43 had inducible ventricular tachycardia or fibrillation in the electrophysiologic laboratory as well.

Thirty-five patients in this study had right bundle branch block pattern on their surface electrocardiogram; all were in sinus rhythm. Only two of these patients demonstrated bundle branch reentry; 21, however, developed intraventricular reentrant complexes. Of 17 patients with left bundle branch block, only one had bundle branch reentry and eight had intraventricular reentry.

Discussion

Repetitive ventricular responses are a frequent accompaniment of ventricular stimulation. Such repetitive responses were noted in 59.5% of 400 consecutively studied patients. The most common form of repetitive response was that due to bundle branch reentry. As suggested by previous workers,[1] bundle branch reentry was observed in normal individuals as frequently as it was in those with organic heart disease. Wellens and colleagues[3] and Josephson and associates[4] observed that bundle branch reentry rarely if ever caused sustained ventricular tachycardia, and this was true in the present study, in which no patient developed sustained bundle branch reentry as the mechanism of sustained ventricular tachycardia. Thus macroentry involving the bundle branches (the mechanism postulated for bundle branch reentry) does not appear to be a cause of sustained spontaneous or induced ventricular arrhythmias. However, bundle branch reentrant complexes may act as additional extrastimuli inducing sustained ventricular tachycardia or intraventricular reentry. Wellens and co-workers[3] observed that in six of 29 patients with inducible ventricular tachycardia the initial complex (V_3) was different in morphology from subsequent complexes and in some cases this initial complex was undoubtedly a bundle branch reentry.

Intraventricular reentry appeared far more commonly in patients with organic heart disease than in patients with normal hearts and was associated with the presence of more malignant forms of ventricular dysrhythmias. Of 78 patients with either isolated intraventricular reentry or intraventricular reentry associated with bundle branch reentry, 43 had documented sustained ventricular tachycardia and/or fibrillation. Furthermore, the frequency of intraventricular reentry in patients with significant ventricular arrhythmias was 74%, whereas it was 9.1% in patients without such arrhythmias ($p < 0.001$). While the patient population with intraventricular reentry contained a higher percentage of patients with documented or suspected ventricular tachycardia/fibrillation, the fact that this form of repetitive response, especially when multiple, was to a large extent confined to this group of patients suggests that a relationship between the two does exist.

Intraventricular reentry probably results from reentry within the ventricular myocardium and distal His-Purkinje system. This may occur locally in proximity to the site of stimulation or at a distance and in relation to anatomic or ischemic lesions (especially in the left ventricle). Our data suggest that large segments of the proximal His-Purkinje system are not required. Unlike bundle branch reentry, intraventricular reentry cannot be prevented by appropriately time supraventricular impulses which pre-excite the bundle of His. Furthermore, the dissociation between His bundle electrograms and intraventricular reentrant responses suggests that the proximal His-Purkinje system does not form a portion of the reentrant pathway.

As noted previously, patients with bundle

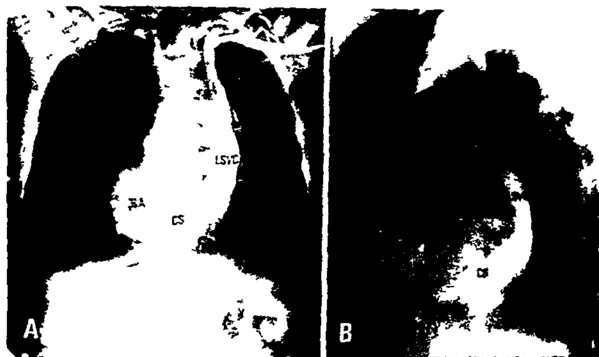


Fig 1 Biplane angiocardiograms of the PLSVC in a 23-year-old female patient with associated ASD *Panel A* is the frontal view and *panel B* is the lateral view The PLSVC is clearly demonstrated both in the frontal and lateral view of the chest. It runs along the left side of the sternum posterior to the left atrium as a narrow tubular shadow Abbreviations *RA* = right atrium *CS* = coronary sinus LSVC = left superior vena cava.

Table 1 Summary of the clinical, hemodynamic and echocardiographic findings in 12 patients with PLSVC

No	Patients	Age	Sex	Complication	Cath.	UCG Tomo	AML E (mm)	AML DDR (mm/s)	AO (mm)	LA (mm)	LVDd (mm)	LVDs (mm)	LVO (mm)	RVO (mm)	EF (%)	O[illegible]
1	M. A.	2?	F	ASD	+	+	26	143	24	3_	35	24	2?	36	6.	+
2	Y M	24	F	ASD	+	+	25	110	17	32	32	25	30	37	52	+
3	N O	4	F	ASD + MI + PAPVR	+	+	23	98	13	33	35	24	26	29	6.	+
4	T S	23	F	MS	+	+	24	29	28	34	50	30	35	24	–	+
5	K. S	37	M	ASD	+	+	25	112	31	30	48	32	32	30	70	–
6	K. M	8	F	–	+	+	18	103	21	21	41	28	24	21	6.	–
7	M K.	4	M	PS + ASD	+	+	19	130	17	23	33	20	22	27	–	–
8	M. A.	3	F	TA	+	+	27	115	20	30	56	47	36	27	41	+
9		6	F	ASD	+	+	20	103	15	18	32	24	30	29	5.	–
10	T H	1	M	ASD	+	+	14	64	15	15	21	14	17	23	70	–
11	T H.	4	M	T F	+	+	16	76	23	16	25	16	22	10	74	+
12	N H.	14	F	ASD	+	+	2	98	23	20	44	30	37	24	6.	+

Abbreviations Cath = catheterization UCG = ultrasonocardiogram, Tomo = cross-sectional echocardiogram, AML = anterior mitral leaflet; E amplitude DDR = diastolic descent rate AO = aorta LA = left atrium LVDd = left ventricular diastolic dimension, LVDs = left ventricular systolic dimension LVO = left ventricular outflow tract RVO = right ventricular outflow tract EF = ejection fraction Op = cardiac operation PAPVR = partial anomalous pulmonary venous return T F = tetralogy of Fallot TA = tricuspid atresia ASD = atrial septal defect; MR = mitral regurgitation. MS = mitral stenosis PS = pulmonary stenosis

diograms of the heart was obtained by two methods (1) a Polaroid camera or an ordinary 35 mm camera was used with a shutter speed of 1 15 sec or in synchrony with the QRS complex of the patient s electrocardiogram (ECG) (2) an 8 mm movie camera was utilized for the continuous recording of the heart movement at 15 frames/sec

The analysis of the cross sectional echocardiograms was carried out on three cross-sectional

Cross-sectional echocardiographic study on persistent left superior vena cava

Norio Hibi M D
Yoichi Fukui M D
Kinya Nishimura M D
Arata Miwa M D
Tadashi Kambe M D
Nobuo Sakamoto M D
Nagoya Japan

Persistent left superior vena cava (PLSVC) is essentially not a serious cardiac malformation producing severe cardiac symptoms by itself However if this lesion can be detected noninvasively the burden on patients would be less at cardiac catheterization and surgical intervention In addition it would be possible to differentiate the abnormalities emanating from the left atrium and/or the boundary between the left ventricle and the left atrium noninvasively

Echocardiography has proved to be useful to analyze the cardiac movement and anatomical abnormalities and to estimate the cardiac function in various congenital and acquired heart diseases Echocardiographic findings of enlarged coronary sinus communicating with an anomalous vein have been reported by a few clinicians using M mode echocardiography but the echo source of the coronary sinus was not fully analyzed In addition a study on PLSVC with cross sectional echocardiography has yet to be reported The purpose of this study is to describe our attempt at the noninvasive diagnosis of the PLSVC using high speed cross sectional echocardiography with mechanical sector scanning combined with an M mode system

From The Third Department of Internal Medicine School of Medicine Nagoya University Nagoya Japan
Received for publication Jan 31 1979
Accepted for publication on March 26 1979
Reprint requests Norio Hibi M D The Third Department of Internal Medicine School of Medicine Nagoya University 65 Tsurumai-cho Showa ku Nagoya Japan 466

Materials and methods

Twelve patients underwent high speed cross sectional echocardiography with a real time mechanical imaging system Ages ranged from 1 to 37 years Four patients were male and eight were female Cardiac catheterization combined with angiocardiography was performed on all 12 patients before or after cross sectional echocardiographic examination The main associated cardiac malformations of the examined patients are shown in Table I Seven of the patients underwent surgical repair for main cardiac malformations but the PLSVC was not operated on

Cross sectional and M mode echocardiograms were obtained using a Toshiba Model SSL 51H Sonolayergraph as previously reported by our laboratory This instrument has a 3 MHz 10 mm transducer focused at 75 mm with a repetition rate of 3 6 kHz Sector speed was 30 cross sections per second and sector angle was changed from 30 degrees to a maximum of 90 degrees but it was usually observed with the fixed angle of 80 degrees To enable the identification of the echo source a certain scanning line was manually selected and B mode was switched to M mode to obtain the M mode echocardiogram

The patients were examined in the supine position The transducer was immersed in a castor oil bath placed on the chest surface over the third or the fourth intercostal space at the left sternal border The so called proximity immersed method was employed[6]

The recording of the cross sectional echocar

0002-8703/80/070069 + 08$00 80/0 © 1980 The C V Mosby Co

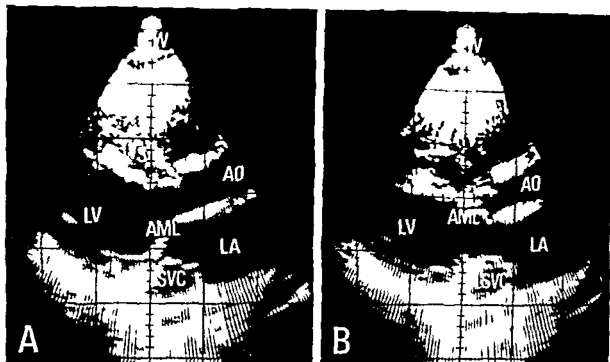


Fig 3 Cross sectional echocardiograms of a long cardiac axis in a 24 year old female patient having PLSVC with ASD *Panel A* is an image of systole and *panel B* is recorded in early diastole An unusual circular echo is recognized at the boundary between the left atrium and the left ventricle Its circular echo shows an almost complete round form Abbreviations *CW* = chest wall *RV* = right ventricle *IVS* = interventricular septum *AO* = aorta *LA* = left atrium *LV* = left ventricle *AML* = anterior mitral leaflet *LSVC* = left superior vena cava

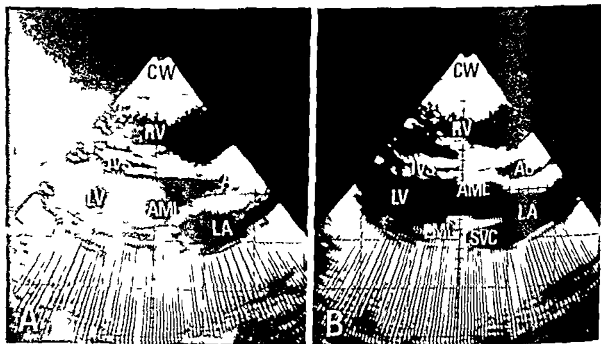


Fig 4 Cross sectional echocardiograms in the long cardiac axis in a 4 year old female patient having PLSVC with ASD and MI *Panel A* is recorded in systole and *panel B* in diastole The circular echo is presented posterior to the PML and it is larger in diastole than in systole The echo discontinuity is recognized at the upper portion of the circular echo Abbreviation *CW* = chest wall *RV* = right ventricle *IVS* = interventricular septum *AO* = aorta *LA* = left atrium *LV* = left ventricle *AML* = anterior mitral leaflet *PML* = posterior mitral leaflet *LSVC* = left superior vena cava

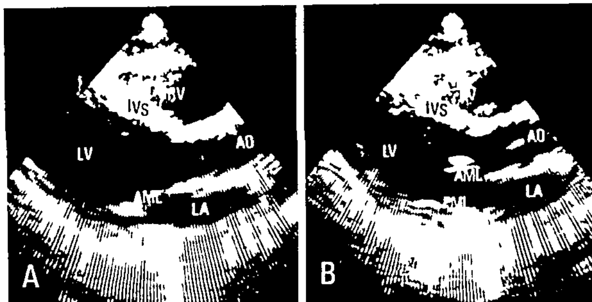


Fig 2 Cross sectional echocardiograms along the long cardiac axis in a normal subject *Panel A* is recorded in systole and *panel B* shows the early diastolic image of the heart The posterosuperior region of the PML is solid wall tissue and revealed no abnormal findings Abbreviations *RV* = right ventricle *AO* = aorta *IVS* = inter ventricular septum *AML* = anterior mitral leaflet *PML* = posterior mitral leaflet *LA* = left atrium *LV* = left ventricle

along the long cardiac axis the sagittal and the horizontal planes of the chest In some patients only one or two cross sections were analyzed

Results

Fig 1 shows the biplane angiocardiograms obtained by the injection of the contrast material from the left subclavian vein in patient No 2 having PLSVC associated with ASD The PLSVC is demonstrated posterior to the left atrium along the left side of the sternum as a narrow tubular image and it opens to the enlarged coronary sinus in the right atrium Thus the PLSVC seems to run along the left atrioventricular sulcus

The cross section of the long cardiac axis demonstrated the relationship between the aorta and two left sided heart chambers The posterior region of the posterior mitral leaflet (PML) usually appears as a solid wall echo in the normal subject (Fig 2) No abnormal echo was recognized at this region

In the patients with PLSVC a circular echo was recognized at the boundary between the left atrium and the left ventricle in the cross section of the long cardiac axis Fig 3 shows the cross sectional echocardiograms along the long cardiac axis in a 24 year old female having PLSVC with ASD A circular echo having an echo free space is clearly demonstrated at the posterosuperior region of the PML In this patient the circular echo has an almost complete form without echo discontinuity According to the real time observation a circular echo was gradually enlarged during systole and it was largest in early diastole at the E point of the anterior mitral leaflet (AML) and contracted in mid diastole In a 4 year old girl with PLSVC the circular echo was also recognized in the same region as in Fig 3 (Fig 4) However the upper part of this echo seems to show an echo discontinuity and to open into the left atrium In the majority of the examined patients the echo discontinuity was recognized at the upper part of the circular echo It is most likely that the echo discontinuity occurred because the echo beam went parallel to the wall of the PLSVC

When the scanning line was selected to the circular echo to obtain the M mode echocardiogram an unusual linear echo with the shallow space was recorded behind the AML Fig 5 presents the M mode scan echocardiograms obtained from patients No 1 2 3 and 6 The AML shows almost normal movement and the diastolic descent rate (DDR) of the AML was also within normal limits The unusual linear echo was demonstrated posterior to the AML but it appeared neither in the left ventricle nor in the left atrium This linear echo gradually moved

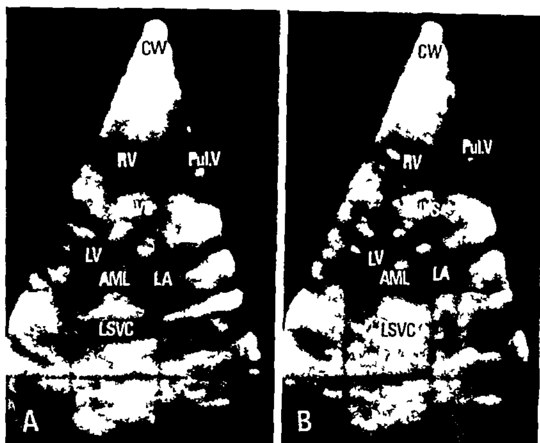


Fig 6 Cross sectional echocardiograms in the patients with PLSVC before (*A*) and after (*B*) dye injection These pictures were recorded along the cross section of the sagittal plane of the chest An echo free space is recognized posterior to the two left sided heart chambers before dye injection (*A*) but the positive contrast echo appears in its echo free space after injection of the indocyanine green from the left medial cubital vein (*B*) Abbreviations *CW* = chest wall *Pul V* = pulmonary valve *RV* = right ventricle *IVS* = interventricular septum *LA* = left atrium *AML* = anterior mitral leaflet *LV* = left ventricle *LSVC* = left superior vena cava

and echocardiographic findings of 12 patients The DDR of the AML was within normal limits except for patient No 5 who had mitral stenosis The amplitude of the AML and aortic dimension (AOD) were both in the normal range The right ventricle was enlarged in the patients with ASD The left atrial dimension (LAD) was mildly enlarged in patients with mitral stenosis and mitral regurgitation An unusual linear echo was recorded in all patients by M mode echocardiography

Discussion

Recently cross sectional echocardiography has developed in various forms as a mechanical and electronic scanning system [1] These methods have made it possible to demonstrate the anatomical abnormalities and to observe the movement of the heart in real time The high speed mechanical sector scanning system reported previously by our laboratory can also be used to observe t cardiac movement and the anatomical abnorm ities in real time

In general the PLSVC was situated at t posteromedial region to the left atrium a opened to the coronary sinus in the right atriu It was clearly demonstrated in the angiocardi grams as a narrow tubular image and was locat at the left atrioventricular sulcus

Echocardiographic findings of the PLSVC ha not been reported but a few studies on enlarg coronary sinus were presented by other a thors There has also been no documentatio on the cross sectional echocardiographic featur of the PLSVC and the enlarged coronary sinu

In our study a circular echo with an echo fr space and a tubular echo were recorded at th posterosuperior region of the mitral valve in th cross section of the long cardiac axis and th sagittal plane of the chest All of the 12 patien

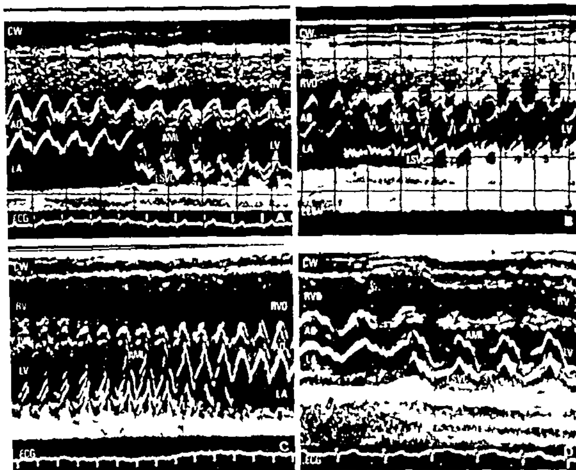


Fig 5 M mode scan echocardiograms in the patients with PLSVC when the transducer was rotated from the aorta to the left ventricle or from the left ventricle to the aorta These pictures were recorded from patients No 1 2 3 and 6 respectively These patients show the abnormal linear echoes posterior to the AML Their movement pattern is slightly changed respectively But these echoes move anteriorly during systole and go back posteriorly in mid diastole An echo free space is recognized posterior to its linear echo Abbreviations *CW* = chest wall *RV* = right ventricle *AO* = aorta *LV* = left ventricle *AML* = anterior mitral leaflet *RVO* = right ventricular outflow tract *LA* = left atrium *LSVC* = left superior vena cava *ECG* = electrocardiogram

anteriorly during systole and retreated posteriorly in diastole Occasionally its movement pattern was similar to that of the AML in some cases It was not considered as an echo of the PML nor as the posterior wall of the left ventricle (LVPW) or that of the left atrium (LVPW) due to the movement and the location Its abnormal linear echo was not detectable in normal subjects and in patients without PLSVC If this echo emanates from the solid tissue the echo free space would not be demonstrable

In the cross sectional echocardiogram through the sagittal plane of the chest a narrow tubular echo was also recognized at the posterior region of the two left sided heart chambers (Fig 6*A*) It was considered to be neither a part of the left ventricle nor the left atrium When the transducer was rotated from the sagittal cross section of the chest to the long cardiac axis it seemed that the circular and tubular echoes emanated from the same lesion

In patient No 2 an injection of indocyanine green was given in the left median cubital vein to confirm the source of the circular echo On the injection of dye the image of the PLSVC was clearly demonstrated as the tubular echo in the sagittal plane of the chest (Fig 6*A*) About one minute after the venous injection the positive contrast echoes appeared in the abnormal cavity (Fig 6*B*) But the upper half was not filled with a cloud of indocyanine green This contrast echo appeared neither in the left ventricle nor in the left atrium

Table I summarizes the clinical hemodynamic

whereas it appeareed neither in the left atrium nor in the left ventricle This abnormal echo was not recognized in normal subjects and other cardiac diseases without PLSVC

In M mode echocardiography, the unusual linear echo was recorded behind the AML It moved anteriorly during systole and went back posteriorly in diastole

Consequently because of the direction of the echo beam the movement and the location of the unusual echo it seems to emanate from the lower part of the PLSVC High speed cross sectional echocardiography has proved to be useful for noninvasive diagnosis of the PLSVC

REFERENCES

1 Gramiak R and Sahn P M Echocardiography of the left ventricular outflow tract and aortic valve *In* Ultra sound in the Diagnosis of Cardiovascular Pulmonary Disease edited by Joyner C R Chicago 1971 Year Book Medical Publishers p 51

2 Aziz K U Paul M H Bharati S Lev M and Shannon K Echocardiographic features of total anom alous pulmonary venous drainage into the coronary sinus *Am J Cardiol* 42 108 1978

3 Nishimura K Hibi N Kambe T Sakamoto N Takemura Y., Nakagawa K and Satoh S High speed ultrasono-cardiotomography Respiration and Circula tion 23 923 1975 (in Japanese)

4 Nishimura K. Hibi N Kato T Fukui, Y Arakawa T Tatematsu H Miwa A Tada H Kambe T Nakagawa K., and Takemura Y Real time observation of cardiac movement and structures in congenital and acquired heart diseases employing high speed ultrasono cardiotomography AM HEART J 92 340 1976

5 Kambe T Nishimura K Hibi, N., Sakakibara T Kato T Fukui, Y Arakawa T Tatematsu H Miwa A. Tada H., and Sakamoto N Clinical application of high speed B mode echocardiography J Clin Ultrasound 5 202 1977

6 Ebina T Oka, S Tanaka M Kosaka S Terasawa, Y Unno K Kikuchi, Y., and Uchida R The ultrasono-tomography for the heart and great vessels in living human subjects by means of ultrasonic reflection tech nique Jap Heart J 8 331 1967

7 Griffith, J M and Henry W L A sector scanner for real time two-dimensional echocardiography Circulation 49 1147 1974

8 King D L. Cardiac ultrasonography Cross-sectional ultrasonic imaging of the heart, Circulation 47 843, 1973

9 Sahn D J Terry R., O Rourke R Leopold G and Friedman W F Multiple crystal cross-sectional echo-cardiography in the diagnosis of cyanotic congenital heart disease Circulation 50 230 1974

10 Lieppe W Scallion R Behar V S and Kisslo J A Two-dimensional echocardiographic findings in atrial septal defect Circulation 56 447 1977

11 Dillon J C., Weyman A E Feigenbaum H Eggleton R. C., and Johnston K W Cross sectional echocardio-graphic examination of the interatrial septum Circula tion 55 115 1977

12 Nishimura K A study on mitral apparatus in mitral stenosis by means of high speed ultrasono-cardiotomog raphy J Clin Med. Ultrasonics 3 81 1976 (in Japa nese)

13 Nichol P M Gilbert B W and Kisslo J A Two-dimensional echocardiographic assessment of mitral ste nosis Circulation 55 120 1977

14 Nimura Y., Matsumoto M Beppu S Matsuo H, Sakakibara H and Abe H Non invasive preoperative diagnosis of cor triatriatum with ultrasono-cardiotomo-gram and conventional echocardiogram AM HEART J 88 240 1974

15 Kerver R E Kelly D H and Gutenkauf C H. Left atrial myxoma Demonstration by stop-action cardiac ultrasonography Am J Cardiol 34 838 1974

16 Hibi N Fukui, Y Nishimura K., Miwa, A and Kambe T Real time observation of left atrial myxoma with high speed B mode echocardiography *J Clin Ultrasound* 7 34 1979

17 Tallury V K. and DePasquale N P Ultrasound cardiography in the diagnosis of left atrial thrombus, Chest 59 501 1971

had the PLSVC opened to the coronary sinus in the right atrium and these abnormal circular and tubular echoes were recognized in all According to the M mode echocardiograms this feature was also shown as an unusual linear echo showing an echo free space posteriorly This is neither the echo of the LVPW nor that of the LAPW since it has an echo free space between the unusual linear echo and more dense structures of the heart wall

It is a matter of controversy as to whether this echo resulting from the enlarged coronary sinus communicates with an anomalous vessel or with the PLSVC itself Gramiak and Sahn[1] reported the echocardiographic findings of the enlarged coronary sinus The same authors recognized an unusual linear echo behind the AML with an echo free space and they stressed that its linear echo moved posteriorly during systole with a resultant narrowing of space followed by a widening in diastole as the margin moved forward In contrast our data showed that the linear echo was gradually enlarged during systole and the anterior margin retreated backward in mid diastole The movement was different in their report and in ours

In this study the transducer was placed at the left side of the sternum in the third or the fourth intercostal space and the echo beam was set to the posteromedial direction perpendicularly through the left atrioventricular sulcus In addition the echo beam went through the left sided margin of the right ventricle and the right ventricle was demonstrated to be a small cavity in the cross section of the long cardiac axis But the right atrium was not recognized in the same cross section On the other hand the right ventricular outflow tract was observed in the cross section of the sagittal plane of the chest but the right atrium and coronary sinus were not recognized However the circular and tubular echoes were clearly recognized posterior to the left sided heart chambers in these cross sections Thus the abnormal echo was considered to emanate from the PLSVC

The positive contrast echo appeared in the abnormal space behind the mitral valve with the injection of indocyanine green from the left median cubital vein But its echo cloud was recognized neither in the left ventricle nor in the left atrium and the circular echo was not considered to derive from the left sided heart chambers It was identified as PLSVC by the movement and the location of the unusual echo and with the contrast echocardiographic technique

The abnormal echoes at the border between the left ventricle and the left atrium and/or in the left atrial chamber should be differentiated from those of PLSVC by echocardiographic examination but they are not always confirmable by M mode echocardiography alone The abnormal echo from these regions was recognized as representing one of the following conditions the posterior mitral leaflet and calcified mitral leaflet in mitral stenosis [11] the diaphragm of the cor triatriatum [1] the mass of the left atrial myxoma [3] the linear or mass echo of the thrombus in the left atrium and thickened chordae tendineae [1] Cross sectional echocardiography served to show a spatial orientation of the heart and these abnormal echoes were clearly observed at the original position Therefore these echoes could be differentiated by this method through their different location movement and characteristics

High speed cross sectional echocardiography has proved useful to the noninvasive diagnosis of the persistent left superior vena cava

Summary

Twelve patients with persistent left superior vena cava (PLSVC) were studied using high speed cross sectional echocardiography with mechanical sector scanning The majority of the examined patients had other associated congenital heart diseases

A circular echo with an echo-free space was demonstrated at the posterosuperior region of the posterior mitral leaflet (PML) in the cross section of the long cardiac axis It was also recognized as a narrow tubular cavity echo posterior to the left atrium and the left ventricle in the cross section of the sagittal plane of the chest This abnormal echo was gradually enlarged during systole and the unusual cavity was largest in early diastole at the E point of the anterior mitral leaflet (AML) and its anterior margin moved back in mid diastole Thus abnormal echo seems to be correspond to the left atrioventricular sulcus By the injection of indocyanine green at the left median cubital vein the positive contrast echo appeared in the cavity which was considered to be PLSVC

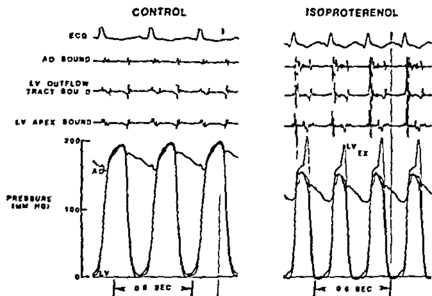


Fig 1 Sound and pressure in the aorta *(AO)* left ventricular *(LV)* outflow tract and LV apex during the control period and during the infusion of isoproterenol During isoproterenol a gradient appeared between the LV apex and outflow tract There was no intraventricular murmur but a murmur did develop distal to the aortic valve

French angiographic catheter tip micromanometer was positioned in the outflow tract of the left ventricle All catheters were made equisensitive

Intracardiac pressure and sound were measured with the same catheter tip transducer as was previously described in detail.[8] Pressure and sound were recorded on an Electronics for Medicine VR 12 photographic recorder at paper speeds of 25 and 250 mm /sec The frequency response of the recording system was flat to 700 Hz with a 3 dB drop at 2100 Hz

A left ventriculogram was obtained with the dog on its left side following the measurement of control pressures and sound Pressures and sound measurements and the ventriculogram were repeated after an intraventricular pressure gradient (> 30 mm Hg) was induced by a constant intravenous infusion of isoproterenol (4 to 8 μg/minute) All ventriculograms were obtained on 35 mm cine film at 60 frames/second

In two dogs intentional entrapment of the tip of the catheter was induced by wedging the catheter in the ventricular trabeculae

Results

Intracardiac measurements of pressure and sound showed no intraventricular pressure gradient or murmurs during the control period The left ventriculogram of all dogs during the control state showed good contraction and no mitral regurgitation

Following the infusion of isoproterenol, an intraventricular pressure gradient that ranged between 47 and 90 mm Hg developed in all dogs No systolic or diastolic murmurs were detected within the left ventricle An ejection murmur was recorded above the aortic valve in all but one dog (Fig 1) The left ventriculogram performed during the infusion of isoproterenol showed almost complete obliteration of the apical region of the left ventricle

In two dogs in which entrapment of the tip of the catheter was induced an intraventricular gradient of 80 mm Hg was observed The left ventriculogram showed a normally contracting left ventricle Recordings of intracardiac sound in both dogs showed no murmurs in the left ventricle or distal to the aortic valve

Discussion

In this study we observed no intraventricular murmur in the obliterating left ventricle despite a prominent intraventricular pressure gradient When a systolic murmur occurred it was distal to the aortic valve These intracardiac sound recordings were strikingly different from those observed in patients with hypertrophic obstructive cardiomyopathy [1, 12] Studies in patients with true ou

Intracardiac phonocardiography in experimental left ventricular cavity obliteration potential clinical applicability for the distinction of obliterating left ventricle from hypertrophic obstructive cardiomyopathy

Hani N Sabbah B S
Mario Marzilli M D *
Paul D Stein M D
Detroit Mich

Left ventricular cavity obliteration may be seen in a spectrum of ventricular disease states[1] It is important to distinguish it from outflow tract obstruction particularly hypertrophic obstructive cardiomyopathy which it may simulate because of differences of treatment The similarity of the clinical features and the hyperdynamic nature of ventricular contractions that are common to both hypertrophic obstructive cardiomyopathy and left ventricular outflow tract obstruction [3] increases the difficulty of differentiation √An intraventricular pressure gradient is generally considered an important diagnostic feature of hypertrophic obstructive cardiomyopathy and other forms of outflow tract obstruction However an intraventricular pressure gradient also occurs in left ventricular cavity obliteration An intraventricular pressure gradient can also appear when the catheter is entrapped in cardiac trabeculae[7]

Because an intraventricular pressure gradient may not actually reflect an outflow tract obstruction it has been suggested that the presence of an intraventricular pressure difference not be accepted as proof of an obstruction without unequivocal proof by other means[1] In view of this other methods for distinguishing between an intraventricular pressure gradient produced by an outflow tract obstruction and a gradient produced by cavity obliteration would be useful We have previously shown that intracardiac sound is useful for identifying subvalvular stenoses and determining the validity of subvalvular pressure *gradients in hypertrophic obstructive cardiomyopathy* subvalvular tunnel stenosis and subvalvular membrane[8] The purpose of this investigation is to describe intracardiac phonocardiography in dogs in which left ventricular cavity obliteration was induced by drugs and to explore the potential use of intracardiac phonocardiography for distinguishing left ventricular cavity obliteration from left ventricular outflow tract obstruction

Methods

Intracardiac pressure and sound were measured in six closed chest mongrel dogs anesthetized with 25 mg/kg intravenous injections of sodium pentobarbital and ventilated with room air A No 6 French catheter tip micromanometer was positioned approximately 1 cm distal to the aortic valve A second No 6 French catheter tip micromanometer was passed retrograde across the aortic valve and positioned as close as possible to the apex of the left ventricle while a No 7

From the Department of Medicine Division of Cardiovascular Medicine and the Department of Surgery Henry Ford Hospital, Detroit
Supported by United States Public Health Service National Heart Lung and Blood Institute grant HL 23669-01
Received for publication May 21 1979
Accepted for publication July 25 1979
Reprint requests Paul D Stein M D Henry Ford Hospital 2799 W Grand Blvd Detroit Mich 48 07
*Visiting Investigator Henry Ford Hospital present address Fisiologia Clinica C N R Via Savi 8 56100 Pisa Italy

0002-8/03/80/070077 + 04$00 40/0 © 1980 The C V Mosby Co

The aortic closure sound in pure aortic insufficiency Circulation 56 859 1977
10 White R I Jr Criley J M Lewis K B and Ross R S Experimental production of intracavitary pressure differences Possible significance of the interpretation of human hemodynamic studies Am J Cardiol 19 806 1967
11 Stein P D Sabbah H N Anbe D T Khaja F and Folger G M Jr Intracardiac sound as a diagnostic adjunct in subaortic stenosis Angiology 30 121 1979
12 Soulie P Joly F and Carlotti J Les stenoses idiopathiques de la chambre de chasse du ventricule gauche Acta Cardiol 17 357 1962
13 Sabbah H N and Stein P D Contribution of semilunar leaflets to turbulent blood flow Biorheology 16 101 1979
14 Sabbah H N and Stein P D Turbulent blood flow in humans Its primary role in the production of ejection murmurs Circ Res 38 513 1976
15 Stein P D and Sabbah H N Turbulent blood flow in the ascending aorta of humans with normal and diseased aortic valves Circ Res 39 58 1976

Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1, 1978 Therefore all manuscripts must be accompanied by the following written statement signed by one author The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C V Mosby Company in the event the work is published The undersigned author warrants that the article is original is not under consideration by another journal and has not been previously published I sign for and accept responsibility for releasing this material on behalf of any and all co authors Authors will be consulted when possible regarding republication of their material



Fig 2 Intracardiac sound aortic *(Ao)* pressure and left ventricular *(LV)* pressure in a patient with hypertrophic obstructive cardiomyopathy *Left* LV catheter was in the apex *Center* LV catheter was within the outflow tract *Right* Both micromanometers were within the aorta The maximal intensity of the murmur occurred within the outflow tract (Reproduced from Henry Ford Hosp Med J 26 35 1978 by permission)

flow tract obstruction (whether due to hypertrophic obstructive cardiomyopathy a subvalvular membrane or a tunnel stenosis) showed that the systolic murmur was of maximal intensity in the outflow tract of the left ventricle distal to the intraventricular obstruction [11, 1] (Fig 2) The subvalvular murmurs were readily detected even when the gradients were small [8, 1]

A pressure gradient measured within the left ventricle may be insufficient to establish a diagnosis of hypertrophic obstructive cardiomyopathy because left ventricular cavity obliteration or catheter entrapment may also cause an intraventricular gradient Therefore additional evidence to support the diagnosis is needed [1] Intracardiac sound may furnish a significant clue to the identification of a true outflow tract obstruction and assist in distinguishing it from cavity obliteration In ventricular cavity obliteration the systolic murmur when present is located distal to the aortic valve and not in the outflow tract of the left ventricle Therefore distinction between true outflow tract obstruction and left ventricular obliteration can be made when simultaneous recordings of intracardiac pressure and sound are made

The murmur generated in dogs with left ventricular cavity obliteration occurred distal to the aortic valve Valvular leaflets act as projections into the stream of flow during systole [3] This results in the breakdown of laminar flow [3] Turbulence distal to the aortic valve would be greatly accentuated in the obliterating ventricle due to the increased blood velocity during ejection [1, 15]

Summary

Intracardiac sound was measured in six dogs four with left ventricular cavity obliteration induced by isoproterenol and two with catheter entrapment In left ventricular cavity obliteration no murmur occurred within the left ventricle Whenever a systolic murmur occurred it was distal to the aortic valve In entrapment no murmur occurred within the left ventricle or distal to the aortic valve Previous studies in patients with hypertrophic obstructive cardiomyopathy showed that the systolic murmur was of greatest intensity within the left ventricular outflow tract Therefore intracardiac phonocardiography may assist in differentiating these conditions which produce an intraventricular pressure gradient

REFERENCES

1 Raizner A E Chahine R A Ishimori, T, and Awdeh M Clinical correlates of left ventricular cavity obliteration Am J Cardiol. 40 303 1977
2 Wilson W S Criley J M and Ross R S Dynamics of left ventricular emptying in hypertrophic subaortic stenosis AM HEART J 73 4 1967
3 Whalen R E Cohen A I Sumner R G and McIntosh H D Demonstration of the dynamic nature of idiopathic hypertrophic subaortic stenosis Am J Cardiol 11 8 1963
4 Cohen, J Effat H Goodwin J F Oakley C M and Steiner R E Hypertrophic obstructive cardiomyopathy Br Heart J 26 16 1964
5 Maron B J Redwood D R Roberts W C Henry W L Morrow A G and Epstein S E Tunnel subaortic stenosis Left ventricular outflow tract obstruction produced by fibromuscular tubular narrowing Circulation 54 404 1976
6 Criley J M Lewis K B White R I, Jr and Ross R S Pressure gradients without obstruction A new concept of Hypertrophic Subaortic Stenosis Circulation 32 881 1965
7 Wigle E D Auger P and Marquis Y Muscular subaortic stenosis Can Med Assoc J 95 793 1966
8 Stein P D Sabbah, H N Anbe D T Khaja F and Folger G M Jr Intracardiac phonocardiography in subaortic stenosis Henry Ford Hosp Med J 26 35 1978
9 Sabbah H N Khaja F Anbe D T and Stein P D

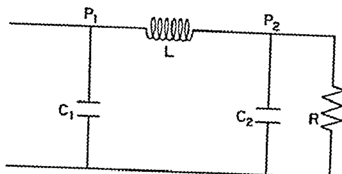


Fig 1 Third-order lumped parameter model (modified Windkessel) of the arterial system used in the pulse contour analysis P_1 = proximal arterial pressure in mm Hg P_2 = distal arterial pressure in mm Hg C_1 = proximal compliance in mL/mm. Hg C_2 = distal compliance in mL/mm Hg L = inertance in mm Hg/mL/sec R = peripheral resistance in mm. Hg/ml /sec

Methods

Animal preparation and instrumentation Eight mongrel dogs weighing from 11 to 30 kg were anesthetized with pentobarbitol 25 mg /kg A 16 gauge 2 inch Teflon catheter (Abbott Cath Abbott Laboratories 4535 16) was inserted percutaneously into the femoral artery and attached directly to a Bell and Howell 4 327 I strain gauge pressure transducer Pressures were recorded on a Hewlett Packard 1064C recorder The frequency response of the total system was flat in terms of amplitude to a frequency of 18 Hz The amplitude began to rise at this point peaked near 35 Hz and fell rapidly for frequencies greater than 35 Hz Heart sounds in a frequency range of 30 to 100 Hz and an ECG were also recorded Duplicate cardiac outputs were measured by the dye dilution method using indocyanine green injected into the central venous circulation while arterial blood was withdrawn through a Gilford cuvette densitometer system Drugs were administered through a short catheter in a foreleg vein

Drug protocol Propranolol was given to limit the heart rate change in response to the vasodilators If initial heart rate was greater than 120 beats/minute propranolol was given to reduce it to 120 beats minute or until 0 5 mg /kg was given If the heart rate was less than 120 beats/minute 0 2 mg kg was given This was done in order to allow a diastolic interval long enough for a sufficient number of points to be sampled for use in the computation routine

The experimental goal during the drug infusions was to infuse a dose that produced a prominent effect on the pressure curve but did not reduce arterial pressure below the physiologic range Sodium nitroprusside (NP) was administered by continuous infusion using a drop counter Prominent effects on the curve shape within the limits of Equation 1 were generally seen with doses of from 2 5 to 10 µg/kg /minute which produced pressure reductions of 20 to 30 mm Hg Nitroglycerin (NTG) was given by continuous infusion on a weight basis Data presented are from dosages of 5 to 10 µg/kg /minute Hydralazine was given by bolus injection in a dose of 1 mg /kg A 30 min period was allowed to reestablish baseline after NP and NTG Hydralazine was given last since its effect is more persistent

Data handling Experimental data consisted of chart recordings of arterial pressures the phonocardiogram and cardiac outputs Data were collected when pressure stabilized on NP after 10 minutes at the particular NTG dose used and 15 minutes after hydralazine injection

Pressure waves were recorded using zero suppression so that pulse pressure covered the full range of the recording scale This reduced the digitization error introduced by the semiautomatic analog to digital conversion done on a Graf Pen (Science Accessories Corporation Southport, Conn) sonic digitizer The digitization system has a resolution of 0 7 mm Hg The output of the sonic digitizer went directly to an IBM 3100 digital computer A sampling rate of 50 samples/sec was used From each set of experimental data three pulses were randomly selected digitized and averaged to form a composite curve that was used by the analysis program The averaging procedure reduced noise levels introduced by the digitization process

The analysis program utilized the portion of the pressure curve occurring after closure of the aortic valve which is interpreted as the transient response of the arterial system to the pressure change occurring in systole This pressure signal was measured at the femoral artery which was considered as point P in Fig 1 The second heart sound (S) was used as a reference in determining the starting point for this transient Watt and Burrus began their analysis at S_2 This however does not take into account pulse wave velocity which must be considered in femoral recordings from dogs particularly when vasodilators are given During these drug infusions we have observed S occurring before the systolic peak in the femoral artery A dicrotic notch remnant on the descending systolic wave was not always visible to serve as a starting point Consequently

Pressure pulse contour analysis in determining the effect of vasodilator drugs on vascular hemodynamic impedance characteristics in dogs

Larry R Zobel M D *
Stanley M Finkelstein Ph D
Peter F Carlyle B S
Jay N Cohn M D
Minneapolis Minn

Vasodilator drugs have been shown to be useful in the treatment of heart failure Therapy results in a rise in cardiac output reduction of peripheral resistance and reduction of pulmonary wedge pressure

A primary purpose of vasodilator therapy is improvement in pump function through a decrease in outflow impedance The outflow impedance imposed by the arterial system consists of resistive inertial and compliant components Systemic vascular resistance calculated from mean arterial pressure and cardiac output does not necessarily provide a valid index to absolute impedance or to changes in impedance The impedance function described by Milnor is a frequency domain determination that requires measurement of instantaneous flow and pressure A time domain approach would in theory also be valid and can be determined in a simplified manner by analysis of the pulse wave contour

Watt and associates have utilized an arterial pulse wave contour to analyze vascular properties in man They observed that the diastolic part of the pressure curve can be fit with a high degree of accuracy to the third order equation

$$P(t) = a_1 \exp(-a\,t) + a_3 \exp(-a\,t)\cos(a_5 t + a_6) \quad (1)$$

The a parameters from this equation describe the configuration of the arterial pressure contour in diastole With knowledge of cardiac output this configuration can be further interpreted using the electrical analog model shown in Fig 1 This circuit is a lumped component model of the arterial system It describes gross mechanical behavior considering the pressure wave after aortic valve closure as a decaying transient response The model components C L C and R cannot be equated with any specific vascular anatomy but have physical meaning by analogy R is the peripheral resistance as traditionally defined C and C represent the lumped compliances of the proximal and distal arteries L represents the lumped inertance that is found in the long columns of blood between the proximal and distal vessels of the arterial system Watt and Burrus[3] found that very similar values for the model components were derived from pressure curves measured at various anatomical locations

In the present study we have utilized the basic method of Watt and Burrus[3] to analyze the vascular effects of sodium nitroprusside nitroglycerin and hydralazine given systemically to normal dogs The data reveal that these vasodilator drugs have different effects on the components that make up total vascular impedance

From the Division of Cardiology Department of Medicine and the Division of Health Computer Sciences, Department of Laboratory Medicine and Pathology University of Minnesota Minneapolis.

Received for publication on July 3 19 9

Accepted for publication Aug 2 19 9

Reprint requests Stanley M Finkelstein Ph.D Division of Health Computer Sciences Box 511 Mayo Memorial Bldg 420 Delaware St S E University of Minnesota Minneapolis MN 55455

*Work performed during tenure as a James F Zagaria Memorial student fellow

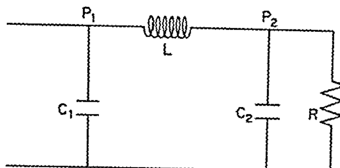


Fig 1 Third order lumped parameter model (modified Windkessel) of the arterial system used in the pulse contour analysis P_1 = proximal arterial pressure in mm Hg P_2 = distal arterial pressure in mm Hg C_1 = proximal compliance in ml/mm Hg C_2 = distal compliance in ml/mm Hg L = inertance in mm Hg/ml/sec R = peripheral resistance in mm Hg/ml/sec

Methods

Animal preparation and instrumentation Eight mongrel dogs weighing from 11 to 30 kg were anesthetized with pentobarbitol 25 mg/kg A 16 gauge 2 inch Teflon catheter (Abbott Cath Abbott Laboratories 4535 16) was inserted percutaneously into the femoral artery and attached directly to a Bell and Howell 4 327 I strain gauge pressure transducer Pressures were recorded on a Hewlett Packard 1064C recorder The frequency response of the total system was flat in terms of amplitude to a frequency of 18 Hz The amplitude began to rise at this point peaked near 35 Hz and fell rapidly for frequencies greater than 35 Hz Heart sounds in a frequency range of 30 to 100 Hz and an ECG were also recorded Duplicate cardiac outputs were measured by the dye dilution method using indocyanine green injected into the central venous circulation while arterial blood was withdrawn through a Gilford cuvette densitometer system Drugs were administered through a short catheter in a foreleg vein

Drug protocol Propranolol was given to limit the heart rate changes in response to the vasodilators If initial heart rate was greater than 120 beats/minute propranolol was given to reduce it to 120 beats minute or until 0 5 mg/kg was given If the heart rate was less than 120 beats/minute 0 2 mg kg was given This was done in order to allow a diastolic interval long enough for a sufficient number of points to be sampled for use in the computation routine

The experimental goal during the drug infusions was to infuse a dose that produced a prominent effect on the pressure curve but did not reduce arterial pressure below the physiologic range Sodium nitroprusside (NP) was administered by continuous infusion using a drop counter Prominent effects on the curve shape within the limits of Equation 1 were generally seen with doses of from 2 5 to 10 μg/kg/minute which produced pressure reductions of 20 to 30 mm Hg Nitroglycerin (NTG) was given by continuous infusion on a weight basis Data presented are from dosages of 5 to 10 μg/kg/minute Hydralazine was given by bolus injection in a dose of 1 mg/kg A 30 min period was allowed to reestablish baseline after NP and NTG Hydralazine was given last since its effect is more persistent

Data handling Experimental data consisted of chart recordings of arterial pressures the phonocardiogram and cardiac outputs Data were collected when pressure stabilized on NP after 10 minutes at the particular NTG dose used and 15 minutes after hydralazine injection

Pressure waves were recorded using zero suppression so that pulse pressure covered the full range of the recording scale This reduced the digitization error introduced by the semiautomatic analog to digital conversion done on a Graf Pen (Science Accessories Corporation Southport Conn) sonic digitizer The digitization system has a resolution of 0 7 mm Hg The output of the sonic digitizer went directly to an IBM 5100 digital computer A sampling rate of 50 samples sec was used From each set of experimental data three pulses were randomly selected digitized and averaged to form a composite curve that was used by the analysis program The averaging procedure reduced noise levels introduced by the digitization process

The analysis program utilized the portion of the pressure curve occurring after closure of the aortic valve which is interpreted as the transient response of the arterial system to the pressure change occurring in systole This pressure signal was measured at the femoral artery which was considered as point P_2 in Fig 1 The second heart sound (S) was used as a reference in determining the starting point for this transient Watt and Burrus began their analysis at S_2 This however does not take into account pulse wave velocity which must be considered in femoral recordings from dogs particularly when vasodilators are given During these drug infusions we have observed S occurring before the systolic peak in the femoral artery A dicrotic notch remnant on the descending systolic wave was not always visible to serve as a starting point Consequently

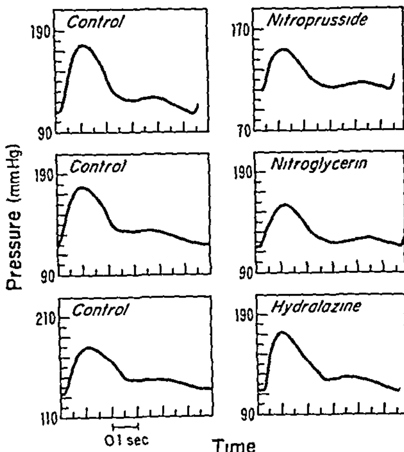


Fig. 2. The effect of vasodilators on the arterial pressure pulse contour. An example from one of the dog experiments reported in this paper is shown.

the time from the end of S_1 to the systolic upstroke was taken as pulse wave transit time. Variations in presystolic ejection time have been considered negligible in comparison to transit time. This transit time was added to the S_2 time to determine the start of pulse wave sampling.

Fitting curves. An iterative curve fitting technique using a Gauss-Newton algorithm was applied (Burrus, personal communication). There are six variables in Equation 1 for which initial guesses are entered. At each iteration the algorithm moves each variable in a direction which reduces the differences between the calculated pressure (from Equation 1) and the actual pressure as measured.

Poor starting guesses for the six variables cause the iteration procedures to diverge. If the change in each a parameter is limited to a part of the calculated correction, the effect of poor initial guesses can be reduced. In practice, step size was limited until the average error was near 3 mm Hg per point. The step size limitation was subsequently removed and the program converged to a minimum value in 2 to 3 additional iterations.

In a few instances when the diastolic wave was broad, the upstroke of the next beat occurred before the pressure at the end point of diastole fell below the pressure minimum between the systolic and diastolic waves. In these cases, the program would not converge unless the pressure curve was extrapolated so that end diastole was below this minimum. The original curves were then fit satisfactorily using the a parameters from the extrapolated curves as initial a guesses. This problem occurred occasionally at high doses of NP and NTG.

Once the a parameters have been determined, it is possible to calculate the time constants RC_1, L/R and RC_2.[7] Peripheral resistance (R) is determined as the ratio of mean arterial pressure to cardiac output. Central venous pressure was considered negligible in this calculation. Model parameters C_1, C_2, and L can then be calculated from the time constants and R. Impedance can be calculated using standard circuit methods.

fits obtainable with Equation 1 indicate that a third-order system can describe the major part of the transient diastolic decay observed in the pressure pulse The transient decay will be determined by characteristics of vessels both proximal and distal to the point of measurement and will depend considerably on the summation of wave reflections in the region of measurement Watt and Burrus[5] found that model components determined from data collected at several different sites along the arterial tree were very similar However it is yet to be determined whether changes in the pulse wave induced by vasodilating drugs are similar at different sampling sites in the arterial tree The model is not meant to be an anatomical model but rather a device to interpret the gross mechanical behavior manifest in pressure measurements

Site of measurement is of consequence in terms of its being proximal or distal. Proximal pressure measurements in man or the dog do not exhibit as prominent a diastolic wave as do distal recordings[11] Bourgeois and associates[1] in fact interpreted the diastolic pressure decay in the thoracic aorta of the dog as a first order system and found its time constant to be proportional to peripheral resistance This would be observed in a Windkessel model with a constant compliance In general curves can be fit to Equation 1 with greater accuracy if the measurement is distal because a diastolic wave is more prominent

Several papers discussed below use frequency domain analysis to evaluate nonresistive components of impedance The use of Fourier analysis to arrive at impedance values as a function of frequency requires few initial assumptions the interpretations of the impedance curves must be based on a particular model Taylor[1] proposed a nonuniform transmission line and then a more elegant model with seventh order branching and nonuniform elasticity In this latter model there is little wave reflection at high frequencies The impedance obtained experimentally at higher frequencies has therefore been interpreted as being representative of the characteristic impedance of the arterial system which depends on its mechanical and geometrical properties The frequency range over which impedance moduli are averaged to obtain a value for characteristic impedance is variable among investigators

Propranolol was given in this study to limit reflex heart rate changes Propranolol does not significantly alter the effects of NP[1] hydralazine[1] or the vasodilatation due to NTG Adams and colleagues[7] measured characteristic impedance in dogs given NP and propranolol although the frequency range they used for this calculation was questionable They did not comment and it was not clear from their results whether propranolol changed the effect of NP on this value We are not aware of studies involving the interaction of propranolol and either NTG or hydralazine with regard to their effects on impedance In the current study propranolol did not completely prevent tachycardia in response to the vasodilating agents This phenomenon has been previously observed[1, 19, 20]

The changes in the a parameters caused by the vasodilators indicate the manner in which they change the pulse contour The significance of these changes may be interpreted using the electrical analog model L (inertance) is determined by properties of blood and the geometry of the vessels and in this case represents effective lumped inertance of a complex geometry Since changes in vessel length and mechanical properties of blood are probably negligible in the present situation a change in L may be assumed to be due to a change in effective mean vascular radius

NTG caused an increase in L, thus suggesting a reduced vascular radius The dominant vascular action of NTG is on the venous bed resulting in decreased venous return to the heart and a fall in cardiac output Since peripheral resistance did not change in the present studies the arterial pressure drop was due to the decreased cardiac output This fall in distending pressure would be expected to passively decrease effective radius and increase L Furthermore Nicolosi and Pieper[3] found that the diameter of the aorta at any given pressure was decreased if venous return was decreased This response could be abolished with alpha blockade or spinal cord transection The reflex sympathetic discharge could be an additional factor in explaining the increase in L noted after NTG Since L is proportional to the inverse of the radius squared a small change in radius could considerably alter L.

The effect of hydralazine is confined to the arterial vascular bed The fall in distending pressure after administration of the drug was due to a decrease in peripheral resistance Inertance was not changed after hydralazine perhaps ...

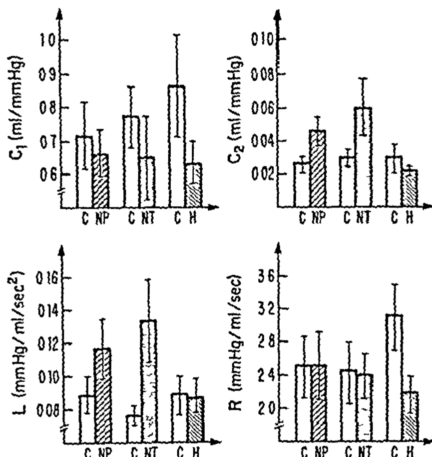


Fig. 3. Variation of circuit parameters for modified Windkessel representation. Data taken from summary in Table I showing mean ± standard error.

frequency domain studies. Clearly, one cannot expect to reproduce impedance functions found from Fourier analysis of pressure and flow signals using a simple lumped parameter model. Impedance moduli determined from our results decreased monotonically with frequency. The reason this occurs in this third order system is explained by Watt and Burrus. The impedance moduli followed the same general patterns for peripheral vascular impedance at the low end of the frequency scale as those discussed in the literature.

Cardiac output fell after NP and NTG while it rose with hydralazine. Modest changes in heart rate occurred despite the use of propranolol.

Discussion

The purpose of this study was to investigate the effect of vasodilator drugs using a simple vascular model whose components are found from pulse contour analysis and knowledge of cardiac output. A stimulus for the study was the observation of pulse contour changes in humans given vasodilators for heart failure and the question of whether pulse contour analysis might be helpful in evaluating clinical response to this therapy. The canine vascular system is not meant to be a model of that system in human heart failure but rather is an experimental tool to determine whether descriptions of the actions of these drugs are consistent with their known effects.

Before discussing the results, a few remarks should be made about this model. The good curve

Table II. The number of dogs which had the indicated change in model components following drug intervention

Component *changes*	Nitroprusside *study*	Nitroglycerin *study*	Hydralazine *study*
Increased C_1	4/8	4/8	1/7
Increased C_2	8/8	8/8	4/7
Increased L	5/8	8/8	2/7
Decreased R	5/8	6/8	7/7

C_1 = proximal compliance; C_2 = distal compliance; L = inertance; R = peripheral resistance.

arterial vasculature was used as a guide in interpreting the observed contour changes The pressure curve during diastole has been viewed as the transient response of the arterial system and can be fit accurately to the equation

$$P(t) = a_1 \exp(-a_2 t) + a_3 \exp(-a_4 t) \cos(a_5 t + a_6)$$

The parameters in this equation and peripheral resistance were used to define the components of the third order Windkessel model consisting of proximal (C_1) and distal (C_2) compliances, an inertance term (L) and peripheral resistance (R) This model describes the gross mechanical behavior seen in the arterial system during diastole The arterial pressure pulse, mean pressure and cardiac output responses to intravenous administration of sodium nitroprusside (NP) nitroglycerin (NTG) and hydralazine (H) were studied using computerized parameter estimating techniques to determine the a_i parameters in the pressure equation and their relationship to the Windkessel components All three drugs caused C to decrease but not significantly NTG increased inertance from 0 076 to 0 134 mm Hg/ml/sec with a p value $< 0\ 05$ NP increased C from 0 027 to 0 046 ml/mm Hg ($p < 0\ 01$) NTG also increased C from 0 030 to 0 060 ml/mm Hg ($p < 0\ 05$) Hydralazine had no significant effect on C but it did reduce R from 3 10 to 2 16 mm Hg/ml/sec ($p < 0\ 01$) Neither NP nor NTG showed a significant decrease in R Thus the three vasodilators apparently have different vascular effects as demonstrated by the pulse contour analysis Such an analysis may be a useful way to evaluate vasodilator therapy

REFERENCES

1 Cohn J N Vasodilator therapy for heart failure The influence of impedance on left ventricular performance Circulation 48 5 1973
2 Cohn J N and Franciosa J A Vasodilator therapy of cardiac disease N Engl J Med 297 27 and 254 1977
3 Chatterjee K and Parmley W The role of vasodilator therapy in heart failure Prog Cardiovas Dis 19 301 1977
4 Milnor W R Arterial impedance as ventricular after load Circ R 36 [illegible]
5 Watt T B [illegible] Arterial pressure contour analysis for [illegible] human vascular properties J Appl Phys 40 [illegible]
6 Watt T B [illegible] the arterial pressure curve [illegible] Research Contractors Conference NASA Manned Spacecraft Center Houston 1964 pp [illegible]
7 Goldwyn R M and W [illegible] Arterial pressure pulse contour analysis via [illegible] model for the clinical quantification of human vascular properties IEEE Trans Biomed Engr 14 11 1967
8 Craige E On the genesis of heart sounds (Editorial) Circulation 53 207 1976
9 Steele R G D and Torrie J H Principles and Procedures of Statistics New York 1960 McGraw Hill Book Company Inc pp 78-80
10 O'Rourke M F and Taylor M G Input impedance of the systemic circulation Circ Res 20 365 1967
11 O Rourke M F The arterial pulse in health and disease Am Heart J 82 687 1971
12 Bourgeois M J Gilbert B K Donald D E, and Wood E H Characteristics of aortic diastolic pressure decay with application to the continuous monitoring of changes in peripheral vascular resistance Circ Res 35 56 1974
13 McDonald D A Frequency dependence of vascular impedance in Pulsatile blood flow Attinger E O ed, New York 1964 McGraw Hill Book Company Inc pp 115 128
14 Taylor M G Wave travel in arteries and the design of the cardiovascular system in Pulsatile blood flow Attinger E O ed New York 1964 McGraw Hill Book Company Inc pp 343 372
15 Taylor M G The input impedance of an assembly of randomly branching elastic tubes Biophys J 6 29 1966
16 Westerhof N Sipkema I Van Den Bos G C and Elzinga G Forward and backward waves in the arterial system Cardiovasc Res 6 648 1972
17 Cox R H Pressure dependence of the mechanical properties of arteries in vivo Am J Physiol 229 1371 1975
18 Poss G and Cole P V Cardiovascular actions of sodium nitroprusside in dogs Anaesthesia 28 499 1973
19 Brunner H Hedwall P R and Meier M Influence of adrenergic beta receptor blockade on the acute cardiovascular effects of hydralazine Br J Pharmacol Chemother 30 123 1967
20 Abboud F M Eckstein J W and Zimmerman B G Venous and arterial responses to stimulation of beta andrenergic receptors Am J Physiol 209(?) 383 1965
21 Ablad B A study of the mechanism of the hemodynamic effects of hydralazine in man Acta Pharmac Tox 20(Suppl 1) 1 1963
22 Adams A P Clarke T N S Edmonds Seal J Foex P Prys Roberts C and Roberts J G The effects of sodium nitroprusside on myocardial contractility and haemodynamics Br J Anaesth 46 80 1974
23 Nicolosi G R and Pieper H P Nature of aortic small muscle responses to changes in venous return in intact dogs Am J Physiol 228 218 1975
24 Moore-Jones D and Perry H M Jr Radioautographic localization of hydralazine 1 C in arterial walls Proc Soc Exp Biol Med 122 576 1966
25 Bergel D H The static elastic properties of the arterial wall J Physiol 156 445 1961
26 Bergel D H Dynamic elastic properties of the arterial wall J Physiol 156 458 1961
27 Nichols W W Conti R C Walker W E and Milnor W R The input impedance of the systemic circulation in man Circ Res 40 451 1977
28 Cox R H and Bagshaw R J Baroreceptor reflex control of arterial hemodynamics in the dog Circ Res 37 772 1975
29 Bagshaw R J Cox R H and Campbell K B Sodium nitroprusside and regional haemodynamics in the dog Br J Anaesth 49 [illegible] 1977

part because it might directly dilate some of the vessels that influence L. Indeed, the drug has been found to localize in the walls of muscular arteries.[24] Proximally, where more elastic tissue is present, radius may be decreased because of less distending pressure and a balance of these effects could lead to a constant L. NP has effects on both venous and arterial vessels, and we observed a nonsignificant increase in L that would be consistent with a summation of the above effects.

Significant changes in proximal arterial compliance were not observed with any of the drugs. According to Bergel's data on the static and dynamic viscoelastic properties of arteries, particularly proximal arteries, compliance should increase when pressure is reduced. In man, Nichols and co-workers found differences in ascending aortic characteristic impedance between two groups of patients with coronary artery disease who had different blood pressures. The group with higher pressure had higher characteristic impedance. In the dog, however, O'Rourke and Taylor[10] did not observe an increase in aortic characteristic impedance when they gave norepinephrine. Cox found that in the dog, characteristic impedance in the thoracic and abdominal aorta, brachial, subclavian, carotid, and femoral arteries was independent of mean pressure in the range of 80 to 150 mm Hg. Cox and Bagshaw perfused the carotid sinus independently and found that ascending aortic characteristic impedance increased when carotid sinus pressure was either increased or decreased from a normalized value, while characteristic impedance in several regional beds varied inversely with changes in carotid sinus perfusion pressure. Since characteristic impedance is determined by both compliance and inertance, a decrease in pressure may have opposite effects on these separate parameters and could therefore result in a variable change in characteristic impedance. In our model, impedance is largely determined by proximal compliance. It seems likely that arterial compliance is the result of various factors superimposed on inherent elasticity and, at least in the dog, it does not appear that changes in pressure have a dominant effect on compliance.

The effect of NP on characteristic impedance in dogs has been studied by Adams and associates and by Bagshaw and colleagues. The calculation of this quantity by Adams and associates may be questionable since it included some low frequencies. Both studies found that characteristic impedance increased in the aorta during NP infusion. In the model used here the impedance seen by the heart at frequencies greater than zero is largely determined by proximal compliance, since it is in parallel with a much larger impedance. This proximal compliance showed an average but nonsignificant decrease with NP. This decrease in C resulted in an increase in the impedance moduli calculated from our model in any frequency range above zero. Therefore these results, using analysis of the pulse wave contour, are compatible with previous studies using Fourier analysis of pressure and flow. We are not aware of any similar studies carried out using NTG or hydralazine with which to compare our results.

In the distal circulation we found that the actions of NP and NTG are different from those of hydralazine. NP has been observed to decrease characteristic impedance in regional beds, an effect which is consistent with the increase in distal compliance in our studies. We did not observe a change in peripheral resistance after NP, a response that is not unexpected in the normal circulation.

Our results imply that NP and NTG reduce distal vessel stiffness, whereas hydralazine increases distal vessel diameter without changing stiffness. We do not have enough information to determine whether these results are due to direct drug actions, are a result of reflex effects on the vascular system, or are due to a combination of these effects.

In human heart failure the arterial system is in a constricted state.[1] This constriction puts a further load on the heart and may lead to a further decrease in cardiac output. Vasodilators interrupt this cycle. It may be helpful when evaluating patients for this therapy to have information about impedance in addition to the other data usually obtained. The technique used in this study is a possible approach to obtain this information. Thus the form of the diastolic wave may provide clinically useful information on the state of the vascular bed. A study to examine vascular parameters in patients with heart failure before and after NP is currently under way.

Summary

The effects of three vasodilators on the shape of the arterial pressure contour in the dog were investigated. A modified Windkessel model of the

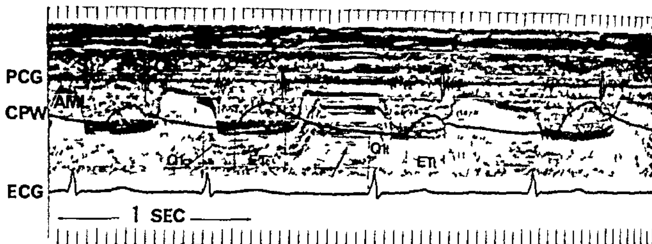


Fig 1 The echocardiogram of the mitral valve with simultaneous electrocardiogram *(ECG)* phonocardiogram *(PCG)* and carotid pulse wave *(CPW)* at a paper speed of 100 mm /sec The diastolic descent rate of the anterior mitral leaflet is abnormally low (30 mm /sec) The tumor echoes are seen *(arrow)* in the second cardiac cycle behind the mitral cusp and disappear quickly at the beginning of ventricular systole An opening snap *(OS)* is noted as the anterior mitral leaflet *(AML)* reaches its maximal anterior excursion The preceding R R interval of the second beat is 710 msec QI interval *(QIc)* and ejection time *(ETc)* are 80 msec and 275 msec respectively The third beat has a much longer preceding R R interval (880 msec) However because of the mitral orifice obstruction by the tumor disproportionate prolongation of the QI interval (*QIt* = 120 msec) and shortening of the ejection time (*ETt* = 200 msec) are noted S = first heart sound S = second heart sound

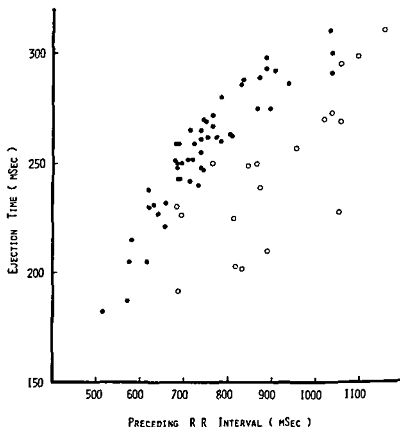


Fig 2 The relation between the preceding R R interval and ejection time *Closed circles* represent the ejection time *with no preceding tumor echoes in the valve orifice Open circles represent the ejection* time just after the appearance of the tumor echoes A logarithmic correlation ($y = -0.871 + 0.170 \ln x$ $r = 0.91$ $n = 59$) is found between the preceding R R interval and the ejection time with no preceding tumor echoes Significant reduction of the ejection time is seen after the appearance of tumor echoes in the valve orifice

Case reports

Left atrial ball thrombus diagnosed by two-dimensional echocardiography

Kenji Sunagawa, M.D.
Yasuhiko Orita, M.D.
Senichi Tanaka, M.D.
Yutaka Kikuchi, M.D.
Motoomi Nakamura, M.D.
Tsuneo Hirata, M.D.
Fukuoka, Japan

Left atrial ball thrombus is a rare disorder. The diagnosis of this serious yet curable lesion has been known to be difficult without cardiac catheterization and angiocardiography.* Although M-mode echocardiography has proven useful in diagnosing left atrial tumors, detection of a ball thrombus in the left atrium is difficult by the conventional technique because of unpredictable motion of the thrombus. Two-dimensional echocardiography allows continuous observation of moving structures with good anatomical orientation in selected cross sections. We report a case of left atrial ball thrombus diagnosed by two-dimensional echocardiography and also describe some of the phonocardiographic and hemodynamic features.

Patient summary

A 55-year-old woman was admitted in January 1976 with a history of recurrent systemic embolization since 1968. She was found to have had a heart murmur in her mid thirties but was asymptomatic until August 1968 when she had an episode of cerebral emboli followed by fatigue and mild dyspnea on exertion. From 1968 to this admission she had at least eight episodes of arterial embolization.

On admission physical examination revealed a heart rate of 65/minute, at times irregular; blood pressure of 140/80 mm Hg; and respiratory rate of 14/minute. The peripheral pulse in her left leg was diminished. The apical impulse was located in the fifth intercostal space at the midclavicular line, and a right ventricular lift was felt at the left sternal border. The first heart sound was accentuated and the second sound was split normally with accentuation of the pulmonic component. An opening snap was present and was followed by rumbling diastolic murmur over the apex. No significant changes in auscultatory findings occurred with alteration of the patient position. The chest was clear to auscultation.

The electrocardiogram revealed atrial fibrillation with mild right ventricular hypertrophy. Chest x-ray examination demonstrated an enlarged left atrium and dilated pulmonary outflow tract with some evidence of pulmonary vascular congestion. The hematocrit was 34.8% and hemoglobin was 11.2 g/100 ml. The erythrocyte sedimentation rate was increased to 89 mm in one hour. The total plasma protein was normal. Protein electrophoresis showed a slight increase in gamma globlin.

Simultaneous recording of the M-mode echocardiogram with phonocardiogram, carotid pulse wave, and electrocardiogram were performed (Fig. 1). The M-mode echocardiogram revealed a reduced early diastolic descent rate of the anterior mitral leaflet with an increased left atrial

From the Research Institute of Angiocardiology and Cardiovascular Clinic, and the Department of Radiology, Kyushu University School of Medicine, Fukuoka, Japan.

Received for publication Nov. 29, 1978.

Accepted for publication March 19, 1979.

Reprint requests: Kenji Sunagawa, M.D., Dept. of Biomedical Engineering, The Johns Hopkins University School of Medicine, 720 Rutland Ave., Baltimore, Md. 21205.

*Dept. of Radiology, Kyushu University School of Medicine.

0002-8703/80/070089 + 06$00.60/0 © 1980 The C. V. Mosby Co.

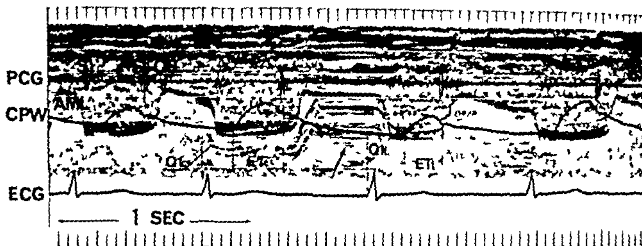


Fig 1 The echocardiogram of the mitral valve with simultaneous electrocardiogram *(ECG)* phonocardiogram *(PCG)* and carotid pulse wave *(CPW)* at a paper speed of 100 mm /sec The diastolic descent rate of the anterior mitral leaflet is abnormally low (30 mm /sec) The tumor echoes are seen *(arrow)* in the second cardiac cycle behind the mitral cusp and disappear quickly at the beginning of ventricular systole An opening snap *(OS)* is noted as the anterior mitral leaflet *(AML)* reaches its maximal anterior excursion The preceding R R interval of the second beat is 710 msec Ql interval *(Qlc)* and ejection time *(ETc)* are 60 msec and 275 msec respectively The third beat has a much longer preceding R R interval (880 msec) However becau e of the mitral orifice obstruction by the tumor disproportionate prolongation of the Ql interval *(Qlt* = 120 msec) and shortening of the ejection time *(ETt* = 200 msec) are noted S = first heart sound S = second heart sound

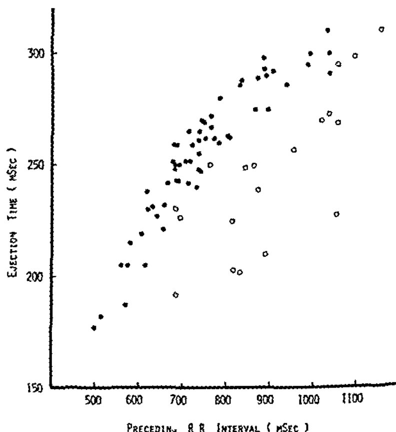


Fig 2 The relatı r between the preceding R R interval and ejection time *Closed circles* represent the ejection time with no precedi tum r echoes in the valve orifice *Open circles* represent the ejection time just after the appearance of the t m r echoes A logarithmic correlation (y = −0.871 + 0 170 ln x r = 0 94 n = 58) is found between the preceding R R interval and the ejection time with no preceding tumor echoes Significant reduction of the ejection time is s n after the appearance of tumor echoes in the valve orifice

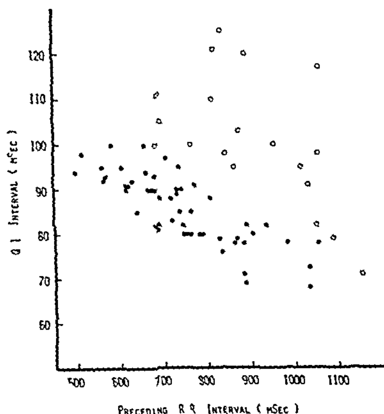


Fig 3 The relation between the preceding R R interval and Q to the first sound interval. *Closed circles* represent the Q to the first sound interval with no preceding tumor echoes *Open circles* represent the Q to the first sound interval after the appearance of tumor echoes. Significant negative correlation (y = 122 – 0 049 x r = 0 80 n = 58) is seen between R R interval and the Q to the first sound interval with no preceding tumor echoes. The Q to the first sound interval is significantly prolonged after the appearance of the tumor echoes in the valve orifice

dimension It also demonstrated tumor echoes *(arrow)* appearing quite sporadically behind the anterior mitral leaflet during diastole and disappearing quickly at the beginning of systole The diastolic descent rate of the mitral valve dropped suddenly from 30 mm /sec to almost zero with the appearance of the tumor echoes in the mitral orifice The phonocardiogram confirmed the presence of the opening snap coincident with the E point of the anterior mitral leaflet An early diastolic plop resulting from abrupt tumor movement [18] was not identified in the beat with tumor echoes A logarithmic correlation was found between the ejection time and the preceding R R interval and Q to the first sound interval was inversely proportional to the preceding R R interval However as can be seen there is a disproportional shortening of the ejection time and a prolongation of Q to the first sound interval in the beat following the appearance of the tumor echoes These findings are summarized in Figs 2 and 3 The apexcardiogram did not show an early systolic notch that was frequently observed in the case of left atrial myxoma [15,18]

The two dimensional echocardiogram was obtained along the long axis of the heart using Aloka SSD 200 (Aloka Co Ltd Japan) Recordings were made with a hand held 60 element 2 25 MHz transducer which provide 200 scanning lines in each cross section at frame rates between 40 to 100/second The effective frame width was 5 cm The multi crystal echocardiography demonstrated (Figs 4 and 5) reduced motion of the mitral cusps and the enlarged left atrium with the essentially normal aortic root and aortic valve leaflets There was a highly mobile spherical tumor in the left atrium without a pedicle attached to the atrial wall The tumor occasionally obstructed the mitral orifice immediately after the opening of the valve and moved back quickly out of the valve orifice into the left atrial cavity at the beginning of ventricular systole

Cardiac catheterization revealed an elevated mean pulmonary capillary pressure of 21 mm Hg

and Eber L. M Echocardiographic diagnosis of a mobile pedunculated tumor in the left ventricular cavity Am J Cardiol. 36 957 1975
13 Feigenbaum H Cardiac tumors *in* Echodiography 2nd ed Philadelphia 1976 Lea & Feiber Publishers chapt 16
14 Farooki, Z Q., Adelman S and Green E W Echocardiographic differentiation of a cystic and a solid tumor of the heart Am J Cardiol 39 107 1977
15 Nasser W K Davis, R H Dillon J C Tavel, M E Helmen C H Feigenbaum H., and Fisch C Atrial myxoma II Phonocardiographic echocardiographic hemodynamic and angiographic features in nine cases AM HEART J 83 810 1972
16 Pitt, A., Pitt, B Schaffer J., and Criley J M Myxoma of the left atrium. Hemodynamic and phonocardiographic consequences of sudden tumor movement Circulation 36 408 1967
17 Craige E Algary W P and Hill C Left atrial myxoma Diagnosis with the help of the phonocardiogram and apex cardiogram Arch. Intern Med. 129 [illegible] 1972
18 Ghahramani A R., Arnold, J R Hildner F J Somm[illegible] L. S and Samet P Left atrial myxoma. Hemodyna[illegible] and phonocardiographic features Am. J Med. 52 [illegible] 1972
19 Kerber R E., Kelly D H., and Gutenkauf C H. L[illegible] atrial myxoma Demonstration by stop action card[illegible] ultrasonography Am J Cardiol 34 831 1974
20 Yoshikawa J Sabah I Yanaghara K., Owaki, Kato H and Tanemoto K Cross-sectional echocardiographic diagnosis of large left atrial tumor and e[illegible] cardiac tumor compressing the left atrium Am J Cardiol. 42 853 1978

Copyright Information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner s consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients This consent is given on the condition however that the copier pay the stated per copy fee through the Copyright Clearance Center Inc 21 Congress Street Salem Mass 01970 617 744 3350 for copying beyond that permitted by Sections 107 or 108 of the U S Copyright Law This consent does not extend to other kinds of copying such as copying for general distribution for advertising or promotional purposes for creating new collective works or for resale

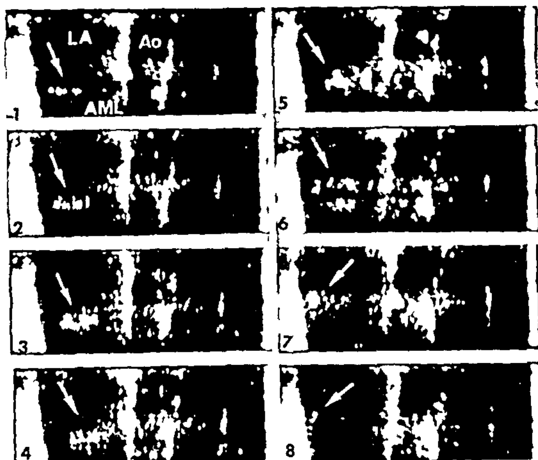


Fig 5 Selected frames (5 cm × 12 cm) from the ultrasonic cross sections obtained along the long axis of the heart (1) (2) Highly mobile pherical tumor (arrow) is seen in the left atrium (LA) measuring 2 cm in diameter There is no pedicle attached to the thrombus The motion of mitral valve is decreased and the LA was enlarged (3) (4) The tumor is approaching to the mitral valve orifice (5) The tumor is obstructing the valve orifice during diastole (6) (7) (8) The tumor moves back quickly to the LA at the beginning of the ventricular systole AML = anterior mitral leaflet Ao = aorta

beat following the appearance of the tumor in the mitral orifice the sudden shortening of the ejection time and the prolongation of Q to the first sound interval were noted Both of these findings are indirect evidence of decreased left ventricular filling associated with an elevated left atrial pressure resulting from the sudden mitral orifice obstruction by the tumor Detailed analysis of the data obtained by the conventional noninvasive techniques could provide critical clues for the diagnosis of the occlusive left atrial tumor

We thank Drs Akira Takeshita and W Lowell Maughan for their valuable comments and discussions in the preparation of this manuscript

REFERENCES

1 Abramson J L Ball thrombus of the heart Ann Clin Med 3 327 1974
2 Covey G W and Crook R Ball thrombus in left auricule Am J Med Sci 175 60 1928
3 Elson J Free ball thrombus of the left auricle Am Heart J 10 190 1934
4 Garvin C F Ball thrombus in the heart Am Heart J 21 371 1940
5 Case records Massachusetts General Hospital Case Number 36171 N Engl J Med 243 668, 1950
6 Daley R Mattingly T W Holt C L Bland E F and White P D Systemic arterial embolism in rheumatic heart disease Am Heart J 42 566 1951
7 Frater R W M You K W and Jordan A Massive atrial thrombus, N Y State J Med 73 654 1973
8 Soloff L A and Zatuchni J The angiocardiographic diagnosis of left atrial thrombosis Circulation 14 25 1956
9 Wofle S B., Popp R L., and Feigenbaum H Diagnosis of atrial tumors by ultrasound Circulation 39 615 1969
10 Peters M N Hall, R J Cooly D A Leachman R D and Garcia E The clinical syndrome of atrial myxoma J A.M.A 230 695 1974
11 Martinez E C Giles T D., and Burch G E Echocardiographic diagnosis of left atrial myxoma Am J Cardiol 33 281 1974
12 Levisman J A MacAlpin R N Abbasi A S Ellis N

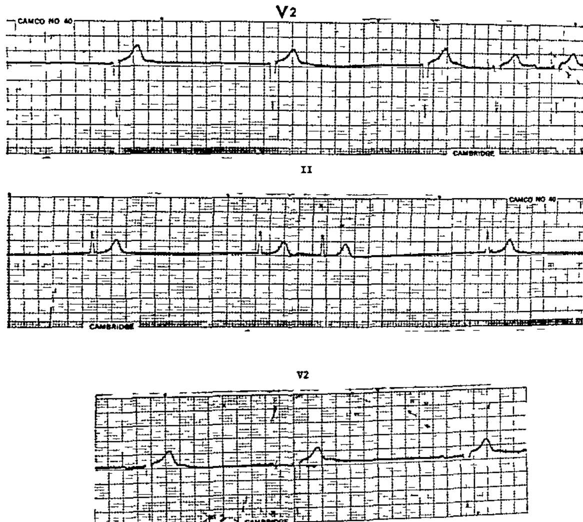


Fig 1B Short rhythm strips from preoperative ECG show junctional rhythm with variable antegrade block occasional sinus capture beats, and a period of profound sinus bradycardia with first-degree AV block

Case report

A 56-year-old white male physician who claimed to be in excellent health his entire life was evaluated medically prior to dental surgery in early January 1978 He denied any cardiac symptoms or signs. Physical examination was normal except for a pulse of 48 beats per minute The patient is a highly trained athlete who for many years has played competitive tennis and has been an avid long-distance runner and cross-country skier His preoperative electrocardiogram (Fig 1) revealed marked sinus bradycardia with a range of 30 to 50 beats per minute An attempt was made to increase the patient's heart rate by vigorous exercise however it rose to only 64 beats per minute A therapeutic trial of atropine 1 mg intravenously increased his heart rate to only 60 beats per minute. The patient underwent 24 hours of Holter electrocardiographic recording and was found to have periods of profound sinus bradycardia as low as 15 beats per minute when asleep as well as occasional sinus pauses and intermittent episodes of junctional rhythm (Figs. 2 and 3) These arrhythmias were felt to be indicative of sick sinus syndrome Although the patient steadfastly denied any symptoms or signs referable to bradycardia it was decided to place a temporary and then permanent transvenous pacemaker

The patient was readmitted to the hospital and monitored overnight during which time his heart rate fell to 11 beats per minute without apparent symptoms (Fig 4) A temporary transvenous pacemaker was inserted via the right femoral vein without difficulty When the tip of the pacing wire reached the right atrium the patient developed asystole lasting approximately 30 seconds A sharp precordial thump restored normal sinus rhythm The pacing wire was then easily advanced across the tricuspid valve and into the apex of the right ventricle without further difficulty Later in the day a permanent pacemaker was installed

Following insertion of the pacemaker the patient noted that he was now more awake and alert during sedentary activities. He then admitted that prior to pacemaker insertion he had been lethargic during periods of rest and inactivity and alert only during active exercise

Discussion

The vast majority of ambulatory active persons with marked sinus bradycardia have typical symptoms of syncope or other obvious evidence of cerebral dysfunction [3] The unique feature of this case is the totally unexpected finding of severe sinus node dysfunction and marked bradycardia

Unusual manifestations of severe sick sinus syndrome

Bruce M Marmor M D F A C P
Martin M Black M D F A C C
Syracuse N Y

The presence of marked sinus bradycardia is usually indicated by symptoms such as dizziness or syncope particularly in active persons Occasionally inactive elderly patients who are asymptomatic are found to have significant sinus node dysfunction with bradycardia on routine electrocardiogram This paper presents a case of an extremely athletic middle aged man who was found to have severe sinus node dysfunction with profound sinus bradycardia and prolonged sinus pauses in the apparent absence of symptoms

Fr m th Sect n f Cardiol gy Depa tm nt of Med n Commun t Gen ral Hosp tal Sy acuse N Y

Rec ed fo publicat on Ma h 9 19 9
A epted for publ cat o Ap 11 19 9

Reprint request Bruce M Marmo M D Dept f C rdiology C mmunity C ral Hosp tal S ra use N Y 13 15

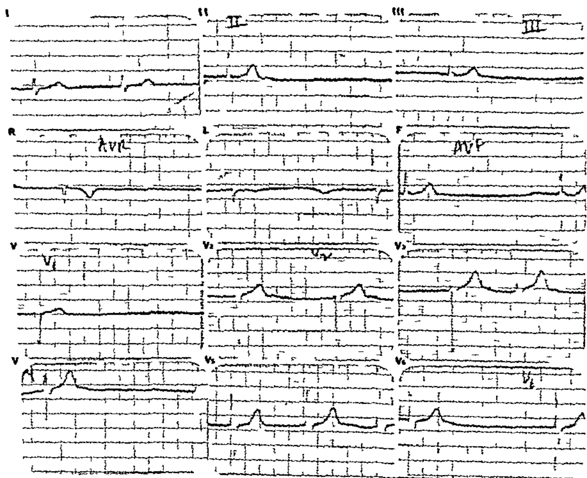


Fig 1A Preoperative electrocardiogram showing junctional rhythm with variable exit block

000' -8 03/80/0 0095 + 04$00 40 0 © 1980 The C V Mosby Co

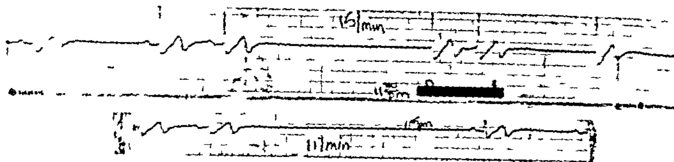


Fig 4 Telemetry strips obtained while the patient was in bed attempting to read a book. *Top strip* shows sinus bradycardia premature atrial beats with capture and sinus arrest terminated by junctional escape beats. *Bottom strip* shows 5½ seconds sinus pause

in a highly trained athlete who denied subtle symptoms until his cardiac function was improved with a pacemaker It appears that he may have been exercising excessively to remain awake and alert through altered autonomic tone We feel, therefore that there is a subgroup of patients with sick sinus syndrome who do not have the typical cerebral symptoms but may rather express a feeling of well being only during active exercise When such symptoms are exhibited we suggest that the patient have ambulatory 24 hour cardiac monitoring in order to demonstrate possible sinus node dysfunction or other bradyarrhythmias

Another important feature of this case was the episode of prolonged sinus arrest occuring when the temporary pacemaker tip reached the right atrium The exact electrophysiological mechanism is unclear however the episode might have been prevented had the patient been given atropine prior to the temporary pacemaker insertion [4] Therefore perhaps patients with severe sick sinus syndrome manifested by markedly prolonged sinus pauses in the range of 4 to 5 seconds should be given a substantial dose of atropine (1 0 to 2 0 ml intravenously) shortly before the insertion of a temporary pacing wire in order to avert prolonged sinus arrest

Summary

An extremely athletic 56-year old male physician was found to have profound sinus bradycardia His only symptom was markedly increased alertness while actively exercising During pacemaker insertion he had an episode of prolonged sinus arrest terminated by a precordial thump This case suggests that exercise can alter autonomic tone and increase cardiac output in sick sinus syndrome causing improvement in possibly unrecognized subtle cerebral symptoms. It also appears that patients with profound sinus bradycardia should be given a substantial dose of atropine prior to pacemaker insertion in an effort to prevent prolonged sinus arrest

REFERENCES

1 Ferrer M I The sick sinus syndrome in atrial disease J.A.M.A 206 645 1968
2 Ferrer M I. The sick sinus syndrome Circulation 47 635 1973
3 Scarpa W J. The sick sinus syndrome AM HEART J 92 648, 1976
4 Rosen K M., Loeb H S Senno M Z. Rahimtoola, S H., and Gunnar R M Cardiac conduction in patients with symptomatic sinus node disease Circulation 43 836 1971

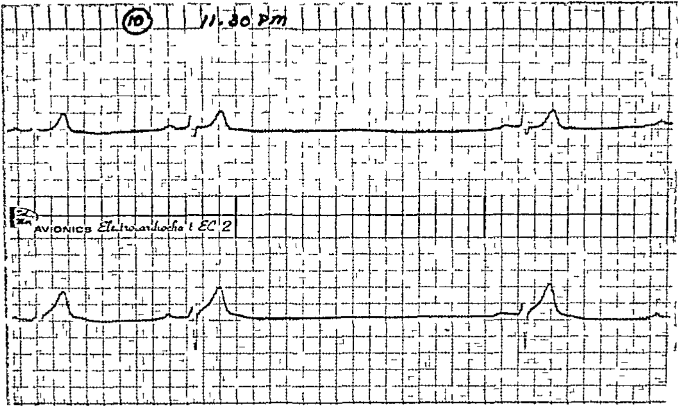


Fig 2 Holter recording shows 4 second sinus pause and first degree atrioventricular block

(16) 7 30 Am
250
200
150
100
50
0
HEART RATE BPM
AVIONICS EC 2
+5
+4
+3
+2
+1
0
-1
-2
-3
-4
-5
S-T LEVEL mm
14271 5

Fig 3 Holter recording during jogging shows accelerated junctional rhythm with occasional atrial capture beats

Table I Initial symptom in 60 patients with giant cell arteritis*

Symptom	Number of patients
Polymyalgia rheumatica	24
Headache	18
Malaise	5
Fever	4
Jaw claudication	3
Scalp nodules	2
Visual loss	2
Aortic arch syndrome	1
Confusion	1
Total	60

*Modified from Reference 6

Table II Clinical findings in 60 patients with giant cell arteritis*

Finding	Group
Sex	
Male No	12
Female No	48
Age at onset, yrs†	69 (51-83)
Duration of disease before treatment months†	6 (½ 24)
With polymyalgia rheumatica No	31
Symptoms related to	
Arteries, No	52
Headache No	31
Jaw claudication No	22
Scalp tenderness No	13
Calf claudication No	4
Arm claudication No	2
Swallowing claudication No	1
Tongue claudication, No	1
Disturbance of vision No	15
Permanent loss of vision No	3
Abnormal arteries on examination No	40

*Modified from Reference 6
†Shown as mean with range in parentheses

malaise fatigue or weight loss Fatigue occurs in nearly all patients and the majority report anorexia and weight loss [5] Constitutional manifestations occasionally are the only findings present and may be attributed by those around the patient to aging or senility Such cases serve as reminders of the need to consider giant cell arteritis in older individuals with failing health Psychosis mental depression and confusion may occur also A low grade fever is frequent and occasionally patients may present as a case of fever of unknown origin

Because of the prominence of these nonspecific symptoms patients sometimes undergo extensive evaluations including exploratory laparotomy to rule out occult malignancy or infection before the presence of giant cell arteritis is realized

Headache is a common initial symptom and is present in up to 90% of patients in some series The headache typically is severe and is localized to the region of the temporal arteries The pain may be constant or intermittent and may be described as boring or lancinating in character However there is such variation in the location and type of pain that giant cell arteritis should be considered in any older patient with a new headache When scalp pain is also present the patient may complain of discomfort combing the hair wearing a hat or laying the head on a pillow

Temporal artery abnormalities are the most helpful physical findings in recognizing giant cell arteritis and are detectable in the majority of patients [3,6] The combination of a tender and swollen or nodular temporal artery in association with other symptoms of arteritis virtually assures the diagnosis (Fig 1) The patient may give a history of recent tender nodules or swelling in the area of the temporal vessels which have resolved by the time the physician is consulted The absence of a pulse in a temporal artery is highly suggestive of arteritis but a subjective difference in the strength of the pulsation between the two sides is generally not a reliable indication of disease

Jaw claudication was felt by Horton [5] to be pathognomonic of temporal arteritis and was associated with involvement of the facial artery It occurs in up to one half to two thirds of patients but its presence may be overlooked if the patient is not specifically questioned about pain or fatigue in the jaw muscles with chewing It must be differentiated from the pain in the temporomandibular joints that develops with a single opening or closing of the mandible A similar type of claudication less commonly occurs in the tongue with chewing or in the muscles of deglutition with repeated swallowing [3]

Polymyalgia rheumatica is defined as aching and stiffness in the neck shoulder girdle and/or hip girdle associated with an elevated erythrocyte sedimentation rate [16,26,27] The pain most commonly is felt in the neck and shoulder girdle but may also be severe in the hip girdle muscles

Review

Giant cell (cranial) arteritis a clinical review

Kent A Huston M D*
Gene G Hunder M D**
Kansas City Mo and Rochester Minn

Giant cell arteritis is a disease of the elderly which when recognized early in its course can be treated effectively with corticosteroids Such treatment results in the relief of symptoms and prevention of blindness or other complications due to occlusion or rupture of involved arteries The term giant cell arteritis has been criticized because giant cells are not found exclusively in this disease and in addition they may be difficult to identify in artery biopsy sections from some patients with typical symptoms Cranial arteritis connotes the most frequent location of the arterial involvement but also has shortcomings because the arteries in the neck and proximal branches of the aortic arch may be affected as well as those of the head Other designations which are used include temporal arteritis granulomatous arteritis polymyalgia arteritica and arteritis of the aged but all also have drawbacks to their usage The first report of the disease was by Hutchinson in 1890[1] who hypothesized that his patient s head pain and inflamed artery was caused by a tight fitting hat That explanation seems humorous today but we cannot yet claim any greater understanding of the etiology The disease was not widely recognized until the classic report of Horton and colleagues in 1932 in which the biopsy findings first were described Since then the clinical spectrum of giant cell arteritis has expanded so that we now recognize its association with polymyalgia rheumatica and include it in the differential diagnosis of headache fever of unknown origin and large vessel arteritis

Epidemiology

Giant cell arteritis is not a rare disorder A recent investigation showed that the prevalence of giant cell arteritis in the population aged 50 years and older was similar to that of ankylosing spondylitis[3] The average annual incidence per 100 000 population aged 50 and older rose from 5 1 in 1950 to 54 to 17 4 in 1970 to 74 probably due to greater recognition of the disease[3] The disease rarely occurs in persons under age 50 years and reaches its greatest incidence in those over age 70[3] In four large series totaling 197 patients 65% were in women[4-7] Giant cell arteritis has been reported mainly in persons of European ancestry but its occurrence in blacks has been noted in several recent case reports[8-10] These observations and several reported instances of familial aggregation suggest that genetic factors may influence its occurrence[3, 7, 11, 12] There is no detectable association between giant cell arteritis and malignancy or other forms of vascular disease[3] Several reported cases have been associated with rheumatoid arthritis but thus far no etiologic association between the two diseases has been established[3, 5, 13-16]

Clinical findings

Tables I and II show the symptoms and findings in a series of 60 patients studied prospectively[6] The *onset* of the illness may be abrupt or insidious A patient may note the rapid development of severe proximal myalgias or headache and swollen temporal arteries[1] But more often the disease begins insidiously with onset of nonspecific *constitutional manifestations* such as

From the Department of Medicine St Luke s Hospital, Kansas City Mo and the Department of Internal Medicine Mayo Clinic and Mayo Medical School, Rochester Minn

Received for publication Feb 9 1979

Reprint requests Kent A Huston M D 4320 Wornall Rd Kansas City Mo 64111

*Dept. of Medicine St. Luke s Hospital and St Luke s Foundation for Medical Education and Research, Kansas City Mo

**Dept. of Internal Medicine Mayo Clinic and Mayo Medical School Rochester Minn

000? 8703/80/070099 + 09$00.90/0 © 1980 The C V Mosby Co

incidental findings in the older age group. Claudication of the upper or less often of the lower extremities and diminished peripheral pulses usually improve with corticosteroid treatment when due to giant cell arteritis. Gangrene of an extremity, ischemic neuropathies and Raynaud's phenomenon are less frequent. An unusually tender carotid or other large artery indicates involvement of that vessel.

Occlusions of large vessels are sometimes found in patients with widespread disease and in some instances aortic rupture and dissection occurs. Aortic valve insufficiency has been reported as a consequence of aortic dissection. Infarctions of the brain and myocardium due to giant cell arteritis have been demonstrated at autopsy in some cases. These complications however are unusual. A recent epidemiologic study showed no increase in occurrence of cardiac disease or stroke in patients with giant cell arteritis over that expected to occur in the general population. Involvement of renal arteries may be found at autopsy and erythrocyte casts may be present in the urine. Renal insufficiency or failure however is rare. Involvement of the aorta and other large vessels is probably much more common than can be detected clinically. In one study medial necrosis of the aorta was found in all five patients with giant cell arteritis coming to autopsy and arteritis was found in 1.7% of 889 consecutive postmortem cases when sections of the temporal arteries and aorta were examined.

Other manifestations of giant cell arteritis which are uncommon but nevertheless of interest are glossitis, recurrent blanching of the tongue, gangrene of the tongue and an altered sense of taste and smell. Scalp necrosis has been reported in a few cases but rarely if ever occurs as a result of temporal artery biopsy.

Laboratory findings

The erythrocyte sedimentation rate is the most helpful laboratory test in the evaluation of giant cell arteritis and is markedly elevated in virtually all patients. For practical purposes the absence of a high erythrocyte sedimentation rate eliminates temporal arteritis from diagnostic consideration although giant cell arteritis has been documented by biopsy in a few patients with a normal or mildly elevated erythrocyte sedimentation rate. A mild normochromic or hypochromic anemia is present in the majority of patients. The hemoglobin concentration is usually in the range of 10 to 12 g/dl but occasionally may be lower. The leukocyte count is usually normal but elevations in the range of 10 000 to 20 000 white cells per mm³ occur in about 40% of patients. The serum protein electrophoresis characteristically reveals an elevated alpha 2 globulin. Liver function tests including glutamic oxalacetic transaminase and alkaline phosphatase levels are elevated in many patients and revert to normal with corticosteroid therapy. Liver biopsies generally are normal or show only mild fatty changes but may show granulomatous hepatitis.

Temporal artery angiography has been used to establish the diagnosis or to identify abnormal segments of the vessel to biopsy. The procedure however is time consuming and may have little advantage over temporal artery biopsy alone. In some cases giant cell arteritis is first recognized by the typical angiographic findings in large vessels showing multiple stenotic areas and occlusions at the end of tapered arterial segments.

The relationship of giant cell arteritis to polymyalgia rheumatica

Whether all patients with polymyalgia rheumatica have the same underlying disease is controversial. Various investigators have found that from 24 to 78% of patients with polymyalgia rheumatica show histologic evidence of vasculitis if their temporal arteries are biopsied. The close association between the two entities has led to speculation that all patients with polymyalgia rheumatica have giant cell arteritis. But this idea has not been universally accepted. The majority of patients with positive biopsies have manifestations of giant cell arteritis other than polymyalgia rheumatica. The crux of the matter is what is the risk of serious vascular complications particularly blindness in patients with pure polymyalgia rheumatica. There is incomplete data to answer this question definitively but the risk of blindness in these patients appears to be relatively small. Many if not most patients with only polymyalgia rheumatica can be satisfactorily treated with non steroidal anti inflammatory drugs or low doses of corticosteroids without ever developing

Characteristically the symptoms disturb sleep and there is an accentuation of soreness and stiffness in the morning Although the patient often describes the discomfort in muscle areas local muscle tenderness is not usually as marked as the pain elicited by movement of the shoulders or hips[7, 8] Other joints particularly the knees and sternoclavicular joints may be swollen[11, 3] Peripheral joint abnormalities when present however are usually mild and transient[11, 1, 3] *Polymyalgia rheumatica occurs in 50% or more of* patients with giant cell arteritis and may be the initial manifestation or may appear for the first time as treatment with corticosteroids is being withdrawn[1] Muscle enzymes electromyograms and muscle biopsies are normal[1, 31] Careful histologic studies have demonstrated inflammatory changes in shoulder synovium capsule bursae and other periarticular structures and joint scanning with technetium pertechnetate has shown increased uptake in the shoulders and other joints[3] These findings suggest that synovitis rather than arteritis or muscle disease is the source of the symptomatology in patients with polymyalgia rheumatica

Visual manifestations are present in 25 to 50% of patients and reflect ischemia of the involved structures[1, 6] Transient visual blurring is not uncommon but by itself may not strongly suggest giant cell arteritis Diplopia occasionally accompanied by ptosis is felt to be secondary to involvement of arteries supplying ocular muscles or cranial nerves but this has not been well studied histologically[6, 6] Partial or complete visual loss is usually permanent but may be preceded by transient blindness[7, 3] The funduscopic picture of ischemic optic neuritis with pallor and swelling of the optic disc often accompanied by small hemorrhages and a few retinal cotton wool patches is seen in the majority of patients with blindness[1] Autopsy studies have demonstrated involvement of the ophthalmic and posterior ciliary arteries in individuals with this ocular complication Less commonly the picture of central retinal artery occlusion is observed and in a few patients central blindness due to infarction of the occipital cortex has been demonstrated[3, 2, 41]

Visual loss is usually associated with clinical abnormalities of the temporal arteries and typically begins abruptly in one eye and progresses over the next few days[39] In individuals with bilateral involvement impairment in the second eye is usually noted a few days or weeks after the initial eye symptoms[39] Blindness rarely develops either as an initial manifestation or after more than one year of disease[4, 4] In one series of 122 patients visual loss was the initial symptom in only two individuals When established the visual deficit rarely improves despite treatment with corticosteroids[47] Even the most encouraging review cited visual improvement with treatment in only 15% of patients[6]

The frequency of blindness reported in patients with giant cell arteritis has decreased since the use of corticosteroids but this may be due at least in part to increased recognition of patients with milder forms of the disease[48] Less commonly reported ocular findings are periorbital edema iritis conjunctivitis and ophthalmomalacia[7, 9] Visual hallucinations and bruits over the orbit may occur and may resolve with corticosteroid treatment[35]



Fig 1 Swelling of both branches of the left superficial temporal artery in a patient with giant cell arteritis Enlargement of a temporal artery to this degree is uncommon From Rodnan G P Mannik M Schumacher H R., Jr eds Primer on the Rheumatic Diseases eighth edition Atlanta The Arthritis Foundation (In press) Reproduced with permission

Large artery involvement is clinically detectable in approximately 10% of patients[3, 50, 51] Bruits are commonly encountered but may be

disease[3] Some biopsies show only intimal proliferation and fragmentation of the internal elastic lamina These milder changes have been termed healed temporal arteritis but may be the only histologic abnormality visible in biopsy specimens from some patients with active disease[3, 11] These latter abnormalities may be differentiated from the normal aging changes of temporal arteries which have been well described in normal and autopsy studies[55, 70]

The most important aspect of the histopathology for the clinician to remember is the occurrence of skip lesions Isolated foci of arteritis have been well documented by serial sections of long segments of involved vessels in 28% of patients[73] In some instances the temporal artery biopsy from one side is normal but the contralateral artery biopsy is positive These findings emphasize the need to obtain a long segment of artery and to examine multiple histologic sections of the specimen If a portion of the vessel is abnormal on clinical examination that segment of course should be biopsied initially If frozen sections from one side are negative in a patient strongly suspected of having arteritis the contralateral temporal artery should be biopsied

The relationship to other forms of vasculitis

There are no clear cut histopathologic differences between giant cell arteritis and Takayasu s disease and there is a considerable overlap in the clinical findings These entities are separated predominantly on the basis of age and epidemiologic differences Takayasu s disease typically occurs in young females and is an arteritis predominately involving large vessels Giant cell arteritis occurs almost exclusively in persons over age 50 and involvement of extracranial large vessels is detected in only a minority of cases Headache and polymyalgia rheumatica are more characteristic of giant cell arteritis and this disease appears to carry a more favorable prognosis Takayasu s arteritis is less responsive to treatment and is sometimes associated with erythema nodosum and hypertension which are not features of giant cell arteritis For these reasons it appears that these are separate entities but a few patients with otherwise typical giant cell arteritis develop large artery involvement and follow a clinical course indistinguishable from Takayasu s disease[2, [illegible]]

Giant cell arteritis is more clearly separated from polyarteritis Though these entities both occur in older individuals the clinical course histopathology, and prognosis are sufficiently different to distinguish between them It should be noted however, that patients with polyarteritis may occasionally have involvement of the temporal arteries[17, 3, 76]

Giant cell granulomatous angiitis of the central nervous system appears to be a separate entity with predominant involvement of the small leptomeningeal and intracerebral arteries and veins The manifestations are severe neurologic changes and the illness is generally progressive and fatal[7]

Diagnosis and treatment

A temporal artery biopsy should be obtained in all patients suspected of having giant cell arteritis including those patients in whom the clinical diagnosis seems certain Although the initial often dramatic improvement with corticosteroids seems to confirm the diagnosis biopsy proof often becomes important later in the course when the clinical picture is blurred because the symptoms are suppressed but the sedimentation rate is above normal and the patient has suffered complications of therapy This is especially true if the physician who is treating the patient is not the one who made the initial diagnosis In these situations subsequent treatment decisions are facilitated if the diagnosis initially was confirmed histologically

Corticosteroid therapy should be instituted when the diagnosis of giant cell arteritis is made In patients in whom the clinical impression of giant cell arteritis is strong prednisone can be started immediately and a temporal artery biopsy can be obtained the following day Small or moderate doses of corticosteroids (10 to 20 mg prednisone per day or equivalent) may alleviate the symptoms within a few days but larger doses are indicated initially to prevent blindness The great majority of patients with giant cell arteritis who lose vision do so before treatment is initiated This in itself speaks strongly for the efficacy of corticosteroids in preventing visual complications The few patients who develop visual loss after starting corticosteroids have usually done so within a few days of starting high doses of corticosteroids or within a few weeks of

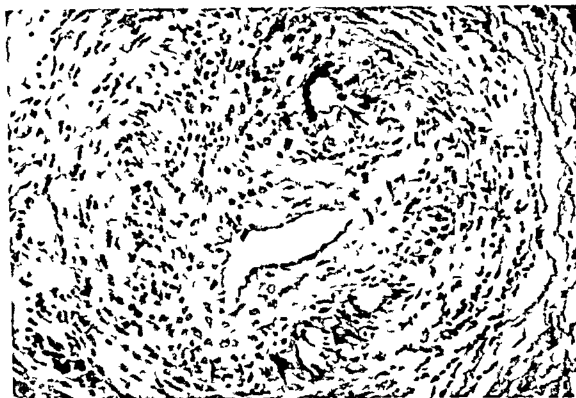


Fig 2 Giant cell arteritis in small branch of temporal artery Multinucleated giant cells *(one pointed out by the arrow)* are present at junction of media and intima There is extensive disruption of all layers of the vessel wall (Hematoxylin and eosin original magnification ×400) From Rodnan G I Mannik M and Schumacher H R Jr eds Primer on the Rheumatic Diseases, eighth edition Atlanta The Arthritis Foundation (In press) Reproduced with permission

vascular complications and with eventual resolution of symptoms The presence of polymyalgia rheumatica alone therefore does not necessitate the use of high dose corticosteroid therapy with its attendant morbidity When steroids are given most patients experience marked relief of symptoms with 5 to 15 mg of prednisone or equivalent per day Even with the use of these low doses of corticosteroids a favorable response is usually so predictable that some authors consider it helpful diagnostically A similar degree of improvement in aching and stiffness may be seen however in patients with rheumatoid arthritis or systemic lupus erythematosus

Whether a patient with polymyalgia rheumatica alone should have a temporal artery biopsy is a decision that needs to be individualized and may be influenced by the severity of the accompanying constitutional symptoms as well as the compliance reliability and general medical condition of the patient The yield of positive temporal artery biopsies is low in patients who after a careful history and physical examination have no other findings suggestive of temporal arteritis Furthermore a negative biopsy does not ensure that a patient will not later develop other manifestations of temporal arteritis Patients treated for polymyalgia rheumatica without a biopsy and those with negative biopsies should be advised to notify their physician if a new headache jaw claudication temporal artery swelling or visual changes develop

Pathology

The characteristic histologic findings of giant cell arteritis are a mononuclear cell inflammatory infiltrate throughout the vessel wall disruption of the internal elastic lamina and the presence of giant cells in the region of the internal elastic lamina (Fig 2) Intimal thickening and thrombosis are additional features The round cell infiltrate in some biopsy specimens may be limited to portions of the wall near the internal elastic lamina Giant cells are not detectable in some cases but their presence or absence does not substantially affect the clinical course of the

9 Goodman L J Layfer L F and Banner B F Polymyalgia rheumatica and giant-cell arteritis in a black woman (Letter to the Editor) N Engl J Med 298 113 1978
10 Sanford R G., and Berney S N Polymyalgia rheumatica and temporal arteritis in blacks—clinical features and HLA typing J Rheumatol 4 435 1977
11 Liang G C Simkin P A Hunder G G Wilske K. R and Healey L A Familial aggregation of polymyalgia rheumatica and giant cell arteritis Arthritis Rheum 17 19 1974
12 Wadman B and Werner I Observations on temporal arteritis Acta Med Scand 192 377 1972
13 Hunder G G Disney T F and Ward L E Polymyalgia rheumatica Mayo Clin Proc 44 849 1969
14 Kalliomaki, J L and Laurén P A Development of temporal arteritis in a patient with rheumatoid arthritis during treatment with indomethacin Acta Rheum Scand 11 131 1965
15 Kogstad O A Polymyalgia rheumatica and its relation to arteritis temporalis Acta Med Scand 178 591 1965
16 Dixon A. St J Beardwell, C., Kay A Wanka J and Wong W T Polymyalgia rheumatica and temporal arteritis Ann Rheum Dis 25 203 1966
17 Hollenhorst R W., Brown J R Wagener H P and Shick, R. M Neurologic aspects of temporal arteritis Neurology (Minneap) 10 490 1960
18 Balmforth, G V Temporal arteritis and renal failure Arch. Intern Med. 113 230 1964
19 Hamrin B Jonsson N., and Hellsten S Polymyalgia arteritica Further clinical and histopathological studies with a report of six autopsy cases Ann. Rheum Dis 27 397 1968
20 Harrison M J G and Bevan A T Early symptoms of temporal arteritis Lancet 2 638 1967
21 Sandok B A Temporal arteritis J.A M A 222 1405 1972
22 Russell, R. W R Giant cell arteritis A review of 35 cases Q J Med 28 471 1959
23 Ghose M K Shensa S and Lerner P I Arteritis of the aged (giant cell arteritis) and fever of unexplained origin Am. J Med. 60 429 1976
24 Paulley J W and Hughes J P Giant cell arteritis or arteritis of the aged Br Med J 2 1562 1960
25 Horton B T Complications of temporal arteritis (Letter to the Editor) Br Med. J 1 105 1966
26 Hunder G G., and Allen G L The relationship between polymyalgia rheumatica and temporal arteritis Geriatrics 28 134 1973
27 Barber H S Myalgic syndrome with constitutional effects. Polymyalgia rheumatica, Ann Rheum Dis 16 230 19,7
28 Polley H F and Hunder G G Rheumatologic interviewing and physical examination of the joints Second edition Philadelphia 1978 W B Saunders Company p 29f
29 Mowat A G., and Hazleman B L Polymyalgia rheumatica—a clinical study with particular reference to arterial disease J Rheumatol 1 190 1974
30 Bruk, M I Articular and vascular manifestations of polymyalgia rhuematica Ann Rheum Dis 26 103 1967
31 Cooke W T., Cloake P C P Govan A D T and Colbeck J C Temporal arteritis a generalized vascular disease Q J Med 15 47 1946
32 Wilske K R., and Healey L A Polymyalgia rheumatica A manifestation of systemic giant-cell arteritis Ann Intern Med 66 77 1967
33 Gordan I Rennie A M and Branwood A W Polymyalgia rheumatica Biopsy studies Ann. Rheum Dis 23 447 1964
34 O Duffy J D Wahner H W and Hunder G G Joint imaging in polymyalgia rheumatica Mayo Clin. Proc 51 519 1976
35 Cullen J F and Coleiro J A Ophthalmic complications of giant cell arteritis Surv Ophthalmol. 20 74 1976
36 Meadows S P Temporal or giant cell arteritis, Proc. R. Soc Med. 59 329 1966
37 Spencer W H and Hoyt W F A fatal case of giant-cell arteritis (temporal or cranial arteritis) with ocular involvement Arch. Ophthalmol 64 862 1960
38 Cullen J F Occult temporal arteritis Trans. Ophthalmol. Soc U K 83 725 1963
39 Wagener H P and Hollenhorst R W The ocular lesions of temporal arteritis Am J Ophthalmol. 45 617 1958
40 Cullen J F Occult temporal arteritis A common cause of blindness in old age Br J Ophthalmol. 51 513, 1967
41 Crompton M R The visual changes in temporal (giant cell) arteritis Report of a case with autopsy findings, Brain 82 377 1959
42 Wilkinson I M S and Russell R W R Arteries of the head and neck in giant cell arteritis A pathological study to show the pattern of arterial involvement Arch. Neurol 27 378 1972
43 Chisholm I H Cortical blindness in cranial arteritis, Br J Ophthalmol 59 332 1975
44 Cohen D N Temporal arteritis Improvement in visual prognosis and management with repeat biopsies, Trans Am Acad Ophthalmol Otolaryngol. 77 74 1973
45 Cullen J F Temporal arteritis Occurrence of ocular complications 7 years after diagnosis, Br J Ophthalmol. 56 584 1972
46 Schneider H A Weber A A., and Ballen P H The visual prognosis in temporal arteritis Ann Ophthalmol. 3 1215 1971
47 Verdich, M., and Nielsen N V *Acute transient* ophthalmomalacia in giant-cell arteritis Report of a case Acta Ophthalmol 53 875 1975
48 Birkhead N C Wagener H P., and Shick, R. M Treatment of temporal arteritis with adrenal corticosteroids Results of fifty five cases in which lesion was proved at biopsy J A M.A 163 821 1957
49 Gibbs, P Temporal arteritis Onset with pseudotumour orbit or red eye *Practitioner 213* 205 1974
50 Gilmour J R Giant-cell chronic arteritis, J Pathol. Bacteriol. 53 263 1941
51 Klein R G Hunder G G., Stanson A W., and Sheps. S G Large artery involvement in giant cell (temporal) arteritis Ann Intern Med 83 806 1975
52 Finlayson R and Robinson J O Giant-cell arteritis of the legs Br Med. J 2 1595 1955
53 McMillan G C *Diffuse* granulomatous aortitis with giant cells Arch. Pathol 49 63 1950
54 Heptinstall R. H., Porter K. A., and Barkley H. Giant-cell (temporal) arteritis, J Pathol. Bacteriol. 67.507 1954
55 Ostberg G On arteritis with special reference to polymyalgia arteritica Acta Pathol. Microbiol. Scand. (A) Suppl. 237 1 1973
56 Grahame R Bluestone R., and Holt P J L. Recurrent blanching of the tongue due to giant cell arteritis, Ann. Intern Med 69 781 1968
57 Hamrin B., Jonsson N., and Landberg T Arteritis in polymyalgia rheumatica, Lancet 1 397 1964

starting treatment with doses equivalent to 5 to 20 mg prednisone per day[3,5,17,18] To minimize vascular occlusion or ruptures 40 to 60 mg of prednisone per day or equivalent is recommended for the first month After that if reversible symptoms have cleared and the tests are normal the dose is gradually tapered using the patient s clinical course the erythrocyte sedimentation rate the alpha 2 globulins and hemoglobin levels as guidelines Most patients require lower doses (10 to 20 mg prednisone per day or equivalent) of corticosteroids for several months[3] Patients with extensive large artery involvement may have a worse prognosis and sometimes require treatment with high dose corticosteroids for a longer period of time than one month In one study over one half of patients required treatment for less than a year[3] Corticosteroids can be discontinued in most patients within two years but a few patients require more prolonged treatment usually because of relapses or lingering symptoms such as headache or musculoskeletal pain which become severe when the corticosteroid dose is further reduced[3] Symptomatic relapses usually occur shortly after the corticosteroid dose is reduced or stopped altogether After a patient has remained asymptomatic for one month or longer off corticosteroids further relapses are infrequent[3] Rarely however patients on long term treatment have developed visual loss This possibility makes it necessary to restart or increase the dose of corticosteroids as soon as a relapse is apparent[7,18] Alternate day corticosteroid treatment has been evaluated in a controlled study of giant cell arteritis and is not as effective as daily therapy Persistent symptoms of polymyalgia rheumatica alone may be adequately controlled with aspirin or other nonsteroidal anti inflammatory drugs so that in many instances prednisone may be reduced further or stopped Histologic evidence of giant cell arteritis may persist in arteries examined several years after the onset of disease but this does not appear to be an indication to continue therapy in the absence of clinical evidence of active disease

Long term follow up of unselected patients has shown that giant cell arteritis has no detectable effect on survivorship[3] This favorable prognosis it should be noted is seen with patients who are treated and the survivorship of untreated patients is unknown It is clear that patients sometimes succumb to the complications of the disease but not with a frequency that significantly affects over all survival

Summary

Giant cell arteritis is a disease of the elderly which is more common than previously recognized It is important to be aware of this condition because treatment effectively relieves symptoms and prevents serious complications The disease is suggested when an elderly patient complains of constitutional symptoms headache jaw claudication or the musculoskeletal manifestations of polymyalgia rheumatica Abnormalities in temporal arteries or other cranial arteries or evidence of large vessel involvement may be detected by physical examination A markedly elevated sedimentation rate in association with other clinical features of the disease strongly suggests giant cell arteritis but a biopsy should be performed to confirm the diagnosis Corticosteroid therapy should be started promptly in high doses in order to prevent blindness Prolonged treatment with lower dose corticosteroids is generally necessary for up to 1 to 2 years and sometimes longer for continued symptomatic relief Long term follow up of treated patients has demonstrated no detectable effect on survivorship

REFERENCES

1 Hutchinson J Diseases of the arteries. On a peculiar form of thrombotic arteritis of the aged which is sometimes productive of gangrene Arch Surg. (London) 1 323 1889 1890
2 Horton B T., Magath T B., and Brown G E An undescribed form of arteritis of the temporal vessels Proc Staff Meet. Mayo Clin 7 700 1932
3 Huston K A., Hunder G G Lie J T., Kennedy R H., and Elveback L R. Temporal arteritis. A 25 year epidemiologic clinical and pathologic study Ann Intern Med. 88 167 1978
4 Hamilton C R Jr., Shelley W M and Tumulty P A Giant cell arteritis Including temporal arteritis and polymyalgia rheumatica Medicine (Baltimore) 50 1 1971
5 Fauchald P Rygvold O and Øystese B Temporal arteritis and polymyalgia rheumatica. Clinical and biopsy findings Ann Intern Med 77 845 1972
6 Hunder G G Sheps S G Allen G L., and Joyce J W Daily and alternate-day corticosteroid regimens in treatment of giant cell arteritis Comparison in a prospective study Ann. Intern Med. 82 613 1975
7 Hamrin B Polymyalgia arteritica Acta Med Scand (Suppl) 533 1 1972
8 Ballou S P., Khan M A and Kushner I Giant-cell arteritis in a black patient Ann. Intern Med 88 659 1978

Difficult problems in the diagnosis of chest pain

Herbert J Levine M D
Boston Mass

Chest pain is not only a common symptom but one which evokes considerable anxiety among patients and clinicians alike In middle aged or older people a new or recurrent pain in the chest or arm is apt to suggest coronary heart disease and the response of a concerned physician is likely to emphasize this possibility As a general rule however while it is in the patient s best interest to err on the side of overdiagnosis of *acute* coronary heart disease there is good reason not to do so with *chronic* chest pain syndromes Failure to recognize acute coronary heart disease could result in a premature death which might have been prevented in an in patient facility However the risk of sudden death from chronic stable coronary heart disease is relatively low Moreover it is not easily prevented and an erroneous diagnosis could easily evoke unnecessary anxiety and have adverse emotional, domestic, and financial consequences Thus a chronic chest pain syndrome particularly one with atypical features for an ischemic origin should always be met with appropriate skepticism with special attention given to those characteristics or findings which do not fit" the pattern of typical angina pectoris Although no physician wishes to be blamed for overlooking the diagnosis of chronic coronary heart disease one of the more rewarding experiences in medical practice is to be able to replace the cloud of coronary disease with a less serious or sometimes quite benign alternative

The differential diagnosis of coronary heart pain includes a wide variety of non-cardiac conditions disease of the esophagus lungs gall bladder osteoarthritis of the upper spine bursitis of joints disease of the muscles tendons or cartilage of the chest wall etc However it is not sufficient merely to establish that the pain is or is not of cardiac origin or even that it is ischemic heart pain Indeed the prognostic implications and frequently the therapy of ischemic heart pain may be substantially different in the patient with hypertrophic cardiomyopathy angina pectoris with normal coronary arteries (Gorlin Likoff syndrome) mitral valve prolapse aortic stenosis, etc vis a vis the patient whose ischemic pain is due to obstructive coronary artery disease. Although regional myocardial ischemia may be common to all of these an accurate etiologic diagnosis is essential for proper management. In most instances the mimics of coronary heart pain present special features which lead the clinician to question the diagnosis of angina pectoris (Table I) In order to take full advantage of these clues a review of the characteristic features of angina pectoris due to coronary artery disease is essential

Angina pectoris

It is generally believed that the basis for angina pectoris is relative myocardial ischemia. Although a specific nerve stimulant produced by ischemia has not yet been identified it is likely that afferent sympathetic nerve endings are activated by a chemical product of ischemia These afferent sympathetic nerves found in the walls of the coronary vessels and in the myocardium carry impulses to the cervical and upper thoracic sympathetic ganglia and then to the spinal cord via the dorsal roots of the first five thoracic segments [1] Considering the potential variations in nerve traffic across this afferent network, the widely variable expression of ischemic heart pain syndromes is not at all unexpected

From the Department of [illegible] Tufts University School of Medicine and New England Medical Center Hospital, Boston, Mass.

Received for publication Oct 1 [illegible] 1979

Reprint requests H. J Levine M D New England Medical Center [illegible] Harrison Ave., Boston Mass 02111

0002-8703/80/070108 + 11$01 10/0 © 1980 The C V Mosby Co

58 Soderstrom C W and Seehafer J R Bilateral scalp necrosis in temporal arteritis A rare complication of Horton s disease Am J Med 61 541 1976
59 Cohen D N., and Damaske M M Temporal arteritis A spectrum of ophthalmic complications Ann Ophthalmol 7 1045 1975
60 Whitaker J J Hagedorn A B., and Pease G L. Anemia in temporal arteritis Postgrad Med 40 35 1966
61 Dickson, E R Maldonado J E., Sheps, S G and Cain J A. Systemic giant-cell arteritis with polymyalgia rheumatica Reversible abnormalities of liver function J.A.M.A 224 1496 1973
62 Hall, G H and Hargreaves T Giant cell arteritis and raised serum alkaline-phosphatase levels (Letter to the Editor) Lancet 2 48 1972
63 Litwack K D., Bohan A and Silverman L. Granulomatous liver disease and giant cell arteritis. Case report and literature review J Rheumatol 4 307 1977
64 Hunder G G Baker H L. Rhoton A. L. Jr Sheps, S G and Ward, L. E Superficial temporal arteriography in patients suspected of having temporal arteritis, Arthritis Rheum 15 561 1972
65 Gillanders L. A Temporal arteriography Clin Radiol. 20 149 1969
66. Stanson A W., Klein R G and Hunder G G Extracranial angiographic findings in giant cell (temporal) arteritis Am J Roentgenol 127 957 1976
67 Alestig K and Barr J Giant-cell arteritis A biopsy study of polymyalgia rheumatica including one case of Takayasu s disease Lancet 1 1228, 1963
68 Healey L. A Parker F and Wilske K R Polymyalgia rheumatica and giant cell arteritis, Arthritis Rheum 14 138 1971
69 Kimmelstiel P Gilmour M T and Hodges H H. Degeneration of elastic fibers in granulomatous giant cell arteritis (temporal arteritis) Arch Pathol. 54 157 1952.
70 Parker F Healey L. A Wilske K R and Odland G F Light and electron microscopic studies on human temporal arteries with special reference to alterations related to senescence atherosclerosis and giant cell arteritis Am J Pathol 79 57 1975
71 Lie J T., Brown A L. Jr., and Carter E T Spectrum of aging changes in temporal arteries Arch Pathol 90 278 1970
72 Reinecke R D and Kuwabara T Temporal arteritis. I Smooth muscle cell involvement Arch Ophthalmol 82 446 1969
73 Klein R G., Campbell, R J Hunder G G., and Carney J A Skip lesions in temporal arteritis, Mayo Clin Proc 51 504 1976
74 Hachiya J Current concepts of Takayasu s arteritis Semin Roentgenol. 5 245 1970
75 Fauci, A S Haynes B F., and Katz P The pectrum of vasculitis. Clinical, pathologic immunologic and therapeutic considerations Ann Intern Med 89 660 1978
76 Morgan G J., and Harris, E D Non giant cell temporal arteritis. Three cases and a review of the literature Arthritis Rheum 21 362 1978
77 Nurick S Blackwood W and Mair W G P Giant cell granulomatous angitis of the central nervous system Brain 95 133 1972
78 Beevers, D G., Harpur J E and Turk K. A. D Giant cell arteritis—the need for prolonged treatment J Chronic Dis 26 571 1973
79 Fulton A. B Lee R V Jampol L. M., Keltner J L., and Albert D M Active giant cell arteritis with cerebral involvement Arch. Ophthalmol. 94 2068 1976

IMPORTANT
INFORMATION FOR AUTHORS

Effective June 1 1980 all manuscripts for the AMERICAN HEART JOURNAL should be sent to

Dean T Mason M D
Section of Cardiovascular Medicine
University of California
School of Medicine
Davis California 95616

nary heart disease but not necessarily to those with acute coronary syndromes Chest pain may last 15 to 20 minutes or more in patients with unstable angina and for hours in the case of frank myocardial infarction

Factors which provoke pain Angina pectoris is generally brought on by physical or emotional stress frequently the combination of the two will provoke pain when either factor alone may not do so Cold weather is a potent factor in evoking angina pectoris by virtue of reflex vasoconstriction of the coronary vessels and as a consequence of the pressor response to cold Isometric hand grip too will provoke angina pectoris in a susceptible individual Indeed the hypertensive and chronotropic response to handgrip probably accounts in large part for the familiar history of angina pectoris developing while a subject carries even a light suitcase at the airline terminal Post prandial angina pectoris is common and occasionally presents as the sole manifestation of ischemic heart pain While the mechanism has been poorly understood recent animal studies suggest that receptors located in the stomach may be responsible for a significant pressor and heart rate response to capsaicin administration Post prandial angina pectoris should be distinguished from abdominal angina While post prandial ischemic pain is the essence of both conditions in the latter ischemic bowel is the source of the pain

According to Gorlin the reproducibility of angina pectoris is surprisingly low in most patients with coronary disease except in subjects with advanced three vessel disease or left main coronary artery obstruction Certainly we are familiar with the first effort phenomenon the individual who experiences angina pectoris on the first fairway of a golf course and then completes the course without pain thereafter Similarly some patients with an unstable form of angina pectoris may develop symptoms with minimal or no provocation—and several weeks later engage in considerable physical exertion without pain with no detectable evidence of an infarction in the interim One very helpful characteristic of angina pectoris is that it is extraordinary for a person suffering from ischemic pain to feel better in the recumbent position The larger cardiac dimensions associated with recumbency increase myocardial oxygen requirements and thus aggravate angina pectoris

Relief of pain Angina pectoris due to coronary artery disease is generally relieved within 1 to 3 minutes by sublingual nitroglycerin Relief following carotid sinus pressure is almost immediate and is dependent upon cardiac slowing[5] Relief of angina pectoris during the Valsalva maneuver occurs during the strain phase (phase 2) of the maneuver and is probably the consequence of a decrease in myocardial wall force (decrease in ventricular pressure and dimensions)[6]

The response of angina pectoris to sublingual nitroglycerin is extremely useful as a diagnostic therapeutic test It should be remembered however that the response must be prompt that is within five minutes and generally less than three minutes Furthermore prompt relief of pain following sublingual nitroglycerin is not diagnostic of angina pectoris Esophageal spasm may be relieved by nitroglycerin and the response to this medication of pain due to spasm of the sphincter of Oddi is often just as dramatic as that of angina pectoris

Physical examination In the absence of congestive heart failure the physical examination is generally not very helpful in confirming the presence of coronary heart disease but it is a crucial procedure in detecting many of the syndromes which masquerade as coronary disease Diastolic filling sounds (S_3 or S_4) are present in less than half of patients with chronic coronary heart disease[7] and thus this finding is of little help in establishing the diagnosis A systolic bulge at or near the apex may be found on palpation and occasionally paradoxical splitting of the S_2 will be detected On the other hand a careful cardiac examination *during* an episode of ischemic heart pain may prove most rewarding A systolic bulge diastolic filling sound paradoxically split S_2 or mitral regurgitant murmur which disappears when the pain subsides is virtually pathognomonic of ischemic heart disease Physical findings suggestive of an underlying metabolic abnormality predisposing to premature atherosclerosis such as skin or tendon xanthomas hypertension diabetic retinopathy etc., are of great importance in the evaluation of patients with chest pain

Electrocardiogram The resting electrocardiogram may be completely normal in as many as 50% of patients with angiographically proven coronary heart disease including those with advanced disease and severe symptoms Of even

Table I

	Chest pain		Dizziness vertigo syncope	Response to		Cardiac auscultation	Abnormal ECG		Stress ECG	Sx reproduced at bedside
	Typical	Atypical		Nitrates	Propranolol		QRS	ST T		
Coronary heart disease	+ + +	+	Rare	+ + + +	+ + + +	– to + + +	common	common	+ + +	–
Angina with normal coronary arteries	+ +	+ +	Rare	+ +	+ +	–	occasional	common	+ + +	–
Hypertrophic cardiomyopathy	+ + +	+	+ +	+	+ + +	– to + + + variable	common	common	+ + +	rare
Mitral valve prolapse	+	+ + +	+ +	+	+ + +	– to + + + variable	rare	common	+ +	rare
Hyperventilation syndrome	+ rare	+ +	+ +	–	+	–	–	rare	+	+ +
Esophageal disease	+ (?)	+ + +	–	+	–	–	–	–	–	–
Radicular syndromes	+	+ + +	+	+ (?)	–	–	–	–	–	+ + +
Chest wall syndromes	–	+ + +	–	–	–	–	–	–	–	+ + +

In eliciting a history of chest pain five specific characteristics of the discomfort are analyzed type of pain location duration factors causing pain and measures which relieve pain

Type of pain Angina pectoris is commonly described as a pressure sensation a tightness or constricting feeling in the chest Common similes include like a band being tightened around my chest or as if someone were standing on my chest Others will describe it as a burning sensation like indigestion It is rarely described as sharp or knifelike Some patients flatly deny that they have any pain whatsoever Instead they complain of a suffocating feeling or shortness of breath which may be misinterpreted as a symptom of pulmonary disease In the author s experience these anginal equivalents are more commonly encountered among older people and in diabetic subjects

It is particularly helpful to observe the patient while the symptom is being described Frequently the patient will curl the fingers into a clenched fist over the sternum as he speaks a sign attributed to the late Dr Samuel Levine Others may press the sides of the chest inwards with both hands as they search for words to characterize the distress In each instance the character of the discomfort varies little with recurrent episodes

Location of pain Most commonly the pain is felt in the center of the chest under the sternum It may be slightly to the left or less often to the right of center Frequently it will radiate to one or both arms particularly the left and more often down the inner rather than the outer surface to *the elbows wrists or occasionally to the fingers* There may be no true arm pain but instead the arms may be described as feeling heavy or numb Not uncommonly the pain will extend into the throat mandible or even the maxilla In other individuals the pain is in the epigastrium or radiates to the back between the scapulae In some extra thoracic pain (i.e arm or jaw) may exist with no chest discomfort whatsoever

The location of angina pectoris varies greatly from one person to another but generally little if at all with recurrent episodes in a given individual Thus a person who complains of chest pain in varying locations on different occasions is not likely to have angina pectoris Another helpful characteristic is that angina pectoris is not well localized If the painful area can be covered with one finger it probably does not represent ischemic heart pain

Duration of pain Patients with chronic angina pectoris due to coronary artery disease generally obtain relief of their pain within 1 to 5 minutes of rest Pain which lasts only several seconds or is fleeting is never due to coronary heart disease Similarly constant pain lasting days or weeks at a time can safely be assumed to be non cardiac in origin It must be emphasized however that these limits apply to patients with *chronic* coro

suggest mitral valve prolapse as a possible etiology, particularly if the resting electrocardiogram reveals no evidence of a conduction abnormality. Chronic fatigue, anxiety, depression, hyperventilation and a variety of symptoms suggesting a neuropsychiatric origin are common in persons with mitral valve prolapse. On the other hand, aside from appropriate concern for their symptoms, the patient with coronary heart disease and *angina pectoris* who has good ventricular function generally feels quite well between episodes of ischemic pain.

Physical examination. When auscultation reveals a typical mid systolic click late systolic murmur, the diagnosis of mitral valve prolapse is easily established. However, the auscultatory findings in this syndrome may be extremely subtle, evanescent, and in some individuals totally *unrevealing even on repeated examinations* ("silent" mitral valve prolapse). Not uncommonly, careful asucultation in the recumbent and standing position is repeatedly negative while subsequently an unmistakable mid systolic click may appear quite inexplicably. If the clinical syndrome is strongly suggestive of mitral valve prolapse, the diagnosis should never be excluded on the basis of one or two negative auscultatory examinations.

Electrocardiogram. Abnormalities of the resting ECG in mitral valve prolapse may be indistinguishable from those observed in either acute or chronic coronary heart disease. When present, the changes most commonly consist of ST segment depression and/or T wave flattening or inversion, particularly in the inferior leads but also in the lateral or right precordial leads.[12] Characteristically, the extent of the repolarization abnormalities may vary considerably, particularly when associated changes in heart rate are observed. The ST-T wave changes of mitral valve prolapse frequently can be differentiated from those of chronic coronary heart disease by their response to a single dose of propranolol.[1] While repolarization changes due to chronic coronary disease change little 1 to 2 hours following a 40 mg tablet of propranolol, the changes due to mitral valve prolapse often are diminished or may disappear. While this response is not specific for mitral valve prolapse,[1, 13] in the proper clinical setting it may be of great help in distinguishing mitral valve prolapse from coronary heart disease.

Other tests. The exercise ECG may reveal a characteristic "ischemic" response particularly in subjects with some repolarization abnormalities on the resting ECG. While a negative exercise myocardial perfusion scan is helpful in excluding significant underlying coronary heart disease, a positive test has been reported in some patients with mitral valve prolapse and normal coronary arteriograms.[16]

Summary. Mitral valve prolapse should be suspected in any patient with atypical chest pain, particularly in a female without important risk factors for atherosclerotic disease. Associated symptoms of palpitations, lightheadedness, syncope, or conspicuous functional symptoms should immediately alert the physician to this diagnosis, and the presence of repolarization abnormalities on the resting and/or exercise ECG should not be *interpreted necessarily as favoring* a diagnosis of coronary heart disease. Repeated auscultatory examinations in the supine, standing, and squatting positions may be necessary to detect the non ejection click or, when present, the dynamic mid late systolic murmur. It should be remembered that there is at present no "gold standard" for establishing this diagnosis, and convincing auscultatory findings should not be "over ruled" by a negative echocardiogram or left ventriculogram.

Hypertrophic cardiomyopathy. Hypertrophic cardiomyopathy (HCM) frequently may masquerade as chronic coronary heart disease, particularly when the dominant symptom is angina pectoris. When HCM is associated with *left ventricular* outflow tract obstruction, a prominent ejection or regurgitant systolic murmur *will alert* the physician to consider a number of conditions other than uncomplicated coronary heart disease. However, the diagnosis of HCM may be especially difficult when little or no outflow tract obstruction is present and the cardiac examination may reveal few clues to the correct diagnosis. While ischemic heart pain due to inappropriate (or appropriate) hypertrophy of the left ventricle is generally indistinguishable from that due to obstructive coronary disease, often there are useful clues which suggest the former process.

Description of pain. Although angina pectoris is a common symptom of HCM, it is reported to be the initial symptom in as few as 10% of symptomatic patients.[17] In the obstructive form

greater importance is the observation that *during* chest pain ST segment depression is only found in approximately half of patients suffering angina pectoris at rest[4] Thus a normal resting electro cardiogram (random or during pain) is not particularly helpful in the differential diagnosis of ischemic heart pain

Stress testing The exercise electrocardiogram has proved extremely useful in the detection of symptomatic coronary heart disease particularly in males However the ability of this test to confirm or exclude coronary heart disease is greatly influenced by the prevalence of this disease in the population under study For example in a recent large multicenter study it was found that a positive stress test increased the likelihood of coronary disease by only 6 to 20% and a negative test decreased the likelihood by only 2 to 28% if the pre test prevalence was estimated on the basis of sex and a description of the chest pain syndrome Expressed differently when the prevalence of coronary disease in high—i e among males with classic angina pectoris—a positive test is highly predictive of coronary heart disease whereas in a group of females with atypical symptoms a negative test is highly predictive of no coronary disease and a positive test would correlate poorly with the presence of coronary disease When exercise electrocardiography is coupled with either myocardial perfusion scanning or radionuclide cineangiography the sensitivity and specificity of stress testing are greatly enhanced

Mimics of coronary heart pain

Chest pain syndromes that masquerade as coronary heart disease generally present one or more characteristics which distinguish them from typical angina pectoris The atypical feature may be a subtle but unmistakable violation in the classic description of Heberden s angina A convincing pain syndrome may come under suspicion because of its rare association with syncope or paroxysmal rapid heart action The electrocardiogram may be inappropriate or the patient s posture may suggest a spinal origin of the symptoms In any case the physician should be particularly alert to unusual aspects of the history or any unexpected findings Among the many conditions that mimic coronary heart pain a number are particularly common offenders

Mitral valve prolapse In some instances the chest pain syndrome associated with mitral valve prolapse may be indistinguishable from that observed in subjects with coronary artery disease that is a typical effort syndrome with all or most of the features of classical angina pectoris More often however there are atypical features which alert the physician to a diagnosis other than coronary heart disease

Description of pain Rest pain is not uncommon The duration of pain frequently is variable—at times consistent with classical angina pectoris while at other times lasting for hours at a time Unlike the situation in the patient with chronic coronary heart disease the location and radiation of the pain may vary in some patients with mitral valve prolapse during recurrent episodes of pain The response to nitrates often is unpredictable—even in the same individual generally prompt relief of pain is not observed following sublingual nitroglycerin In the author s experience subjects with mitral valve prolapse often feel better in the recumbent position when they are having chest pain—a characteristic rarely observed in patients with coronary heart disease This observation is not unexpected when one considers that the relative cardiac dilatation which accompanies recumbency increases wall tension and thus myocardial oxygen requirements aggravating regional ischemia due to coronary disease Mitral valve prolapse on the other hand is reduced as ventricular dimensions are increased and thus recumbency predictably would lessen the mechanical abnormality of prolapse Subjects with mitral valve prolapse who have an effort syndrome suggestive of angina pectoris frequently describe spontaneous variations in the severity of the symptoms that are unrelated to the level of activity They may be relatively free from pain for weeks or months only to experience recurrent bouts of chest pain with relatively little provocation

Associated symptoms While patients with chronic coronary disease and angina pectoris may be subject to ventricular ectopy or paroxysmal rapid heart action palpitations are not generally associated with classic angina pectoris In contrast palpitations are a prominent feature of mitral valve prolapse and commonly coexist with periods of chest pain Certainly recurrent light headedness or particularly syncope in a person with a chest pain syndrome argues against coronary disease as the cause and should immediately

HCM than to any other condition Q waves in the ECG simulating myocardial infarction may be present in the anteroseptal or inferior leads and have been reported in up to half of patients with HCM[18]

Summary In advanced, but as yet unsuspected cases of obstructive HCM the ejection or regurgitant systolic murmur generally leads the physician to consider a valvular lesion which when subsequently evaluated by echocardiography is correctly identified as being due to HCM However in symptomatic individuals with no murmurs or an innocent systolic murmur careful attention to inappropriate findings in the history physical examination and ECG is necessary to distinguish the patient with HCM from one with coronary heart disease Conspicuous dyspnea symptoms of cerebral ischemia, evidence of left ventricular hypertrophy on the ECG and physical examination (particularly in the absence of radiographic evidence of cardiomegaly) an 'inappropriate ECG the absence of risk factors for atherosclerosis—all should suggest the possibility of early HCM in the patient complaining of ischemic heart pain

Esophageal syndromes Esophageal pain is frequently misdiagnosed as ischemic heart disease although the description of pain is rarely that of typical angina pectoris However, there are clinical features shared by both diseases which may seriously confound the diagnosis

Description of pain The common terms used to describe the pain of esophagitis are heartburn warmth fullness pressure distress gnawing a lump—terms quite indistinguishable from those used to describe angina pectoris Among these perhaps the most common is *heartburn* or its *equivalent When this term is used it is helpful* to ask whether the burning sensation more closely resembles *heat* or *acid* The latter response is quite characteristic of esophagitis but is almost never used to describe ischemic heart pain Symptoms of esophagitis generally occur after eating and are often initiated or aggravated by recumbency While this sequence is not particularly common in patients with angina pectoris is it important to remember that with rare exceptions patients with ischemic heart pain too avoid lying flat when they have pain

The distribution of esophageal pain is quite similar to that of angina pectoris Most often it is midline thoracic or abdominal (from the suprasternal notch to the epigastrium) but may extend to the left or right chest the shoulders, arms and hands, the back or throat In one series of ninety six patients discomfort was substernal in 70 per cent abdominal in 67 per cent and radiated to the neck, arms or back in 19 per cent of patients[19] Although exertional pain has been *reported in some patients with esophagitis*[20] the possibility of coexisting coronary heart disease in these patients has not been completely excluded

Esophageal pain simulating ischemic heart pain may also be the consequence of diffuse esophageal spasm or less often achalasia In a group of 43 patients with chest pain and either normal coronary angiograms or negative exercise tolerance tests esophageal manometrics revealed high amplitude non peristaltic contractions in one third of the patients[2] Diffuse esophageal spasm is generally initiated by swallowing particularly of cold liquids, and increased sensitivity to cholinergic drugs and endogenous gastrin may play a role in precipitating symptoms[21] A favorable response to nitrates in subjects with diffuse esophageal spasm further confounds the problem of distinguishing this condition from angina pectoris[4, 5]

Summary Since both esophagitis and coronary heart disease are common conditions, it is expected that the two diseases will frequently coexist Indeed the demonstration that one or both conditions are present does not establish with certainty the cause of a given pain syndrome While endoscopy may indicate that esophagitis is present a positive esophageal acid perfusion test provides further evidence that *esophageal erosion is the source of pain*[19] Similarly chest pain and dysphagia precipitated by swallowing cold liquids and associated with high amplitude non peristaltic esophageal contractions strongly suggest that diffuse esophageal spasm is responsible for the symptoms[21] In the presence of both coronary and esophageal disease provocative tests may be necessary to ascertain the origin of an atypical chest pain syndrome

Radicular syndromes The pain of spinal particularly cervical root compression does not frequently mimic ischemic heart pain Nontheless, in some instances an effort syndrome virtually indistinguishable from angina pectoris may be

of the disease the most common symptom is dyspnea and in one report this proved to be in the initial symptom in 60% of patients [17] Certainly patients with chronic coronary heart disease and angina pectoris may also complain of dyspnea but it is unusual for this symptom to precede the onset of ischemic pain unless it were misinterpreted as an anginal equivalent Thus a careful search for HCM should be made in any individual with angina pectoris who has coexisting or antecedent dyspnea which is not easily explained by transmural infarction cardiomegaly or either regional or diffuse hypokinesis of the ventricle

While the character duration and radiation of ischemic heart pain in HCM and chronic coronary heart disease are quite the same the factors associated with the inception and termination of pain in some instances may be different For example it has been reported that the Valsalva maneuver may effect prompt relief of angina pectoris in subjects with coronary heart disease [6] Since relief of pain occurs during the strain phase of the maneuver it was presumed that a decrease in wall force (decreased ventricular pressure and dimensions) and thus myocardial oxygen requirements was responsible for this phenomenon However in a subject with obstructive HCM outflow tract obstruction is provoked by the Valsalva maneuver and thus the procedure may have quite the opposite effect Occasionally patients with obstructive HCM find that they can obtain relief of their ischemic pain by squatting—a maneuver which increases ventricular dimensions and hence lessens outflow tract obstruction While subjects with HCM often find nitroglycerin useful in terminating episodes of angina an adverse response to nitrates may be observed in those with dynamic outflow obstruction In this circumstance the reduction in ventricular preload brought about by nitrates may precipitate ischemic pain or may evoke symptoms of cardiogenic cerebral ischemia

Associated symptoms As in the case of mitral valve prolapse the association of chest pain with lightheadedness dizziness or syncope should always arouse one s suspicion of HCM Unlike mitral valve prolapse however the chest pain is generally ischemic in character and the symptoms of cerebral ischemia are more apt to be effort related Both atrial and ventricular arrhythmias are common in HCM the latter not infrequently present early in the disease and occasionally the first manifestation of HCM may be a fatal ventricular tachyarrhythmia during strenuous physical exertion Atrial fibrillation tends to be a late complication of HCM and is generally poorly tolerated by the non compliant hypertrophied ventricle

Physical examination The patient with typical ischemic heart pain and a dynamic systolic murmur which is increased in the upright position or during the Valsalva maneuver and which softens during squatting is generally easily identified as having obstructive HCM The real diagnostic challenge is to identify the patient with HCM who has little or no outflow tract obstruction In some such patients no murmur is heard in the supine position but a systolic murmur can be elicited by the appropriate provocative maneuvers In others the only suspicious finding may be a brisk arterial pulse an abnormal left ventricular impulse or an unusually prominent fourth heart sound which frequently may be felt as well as heard

Electrocardiogram Although the ECG was found to be abnormal in all 64 patients with obstructive HCM reported by Braunwald and colleagues [17] in 1964 a normal ECG is not uncommon in patients with mild HCM particularly those with no outflow tract obstruction or those examined early in the course of their disease Generally however the tracing is abnormal most commonly revealing varying degrees of left ventricular hypertrophy intraventricular conduction abnormalities or non specific repolarization changes However much more useful in the evaluation of patients with angina pectoris are those abnormalities which don t quite fit the diagnosis of coronary heart disease For example broad and/or tall P waves suggestive of atrial enlargement are common in HCM and unusual in patients with coronary heart disease A slurred inscription of the R wave (delta wave) with or without a short P R or prolonged QRS interval favors a diagnosis of HCM and this finding too is relatively less common in patients with coronary disease Indeed the ECG in HCM often is best described merely as bizarre

Although electrocardiographic evidence of old transmural myocardial infarction is a hallmark of coronary heart disease this finding in an asymptomatic young individual is more apt to be due to

HCM than to any other condition Q waves in the ECG simulating myocardial infarction may be present in the anteroseptal or inferior leads and have been reported in up to half of patients with HCM [18]

Summary In advanced, but as yet unsuspected cases of obstructive HCM the ejection or regurgitant systolic murmur generally leads the physician to consider a valvular lesion which when subsequently evaluated by echocardiography is correctly identified as being due to HCM However in symptomatic individuals with no murmurs or an innocent systolic murmur careful attention to inappropriate findings in the history physical examination and ECG is necessary to distinguish the patient with HCM from one with coronary heart disease Conspicuous dyspnea symptoms of cerebral ischemia evidence of left ventricular hypertrophy on the ECG and physical examination (particularly in the absence of radiographic evidence of cardiomegaly) an inappropriate ECG the absence of risk factors for atherosclerosis—all should suggest the possibility of early HCM in the patient complaining of ischemic heart pain

Esophageal syndromes Esophageal pain is frequently misdiagnosed as ischemic heart disease although the description of pain is rarely that of typical angina pectoris However there are clinical features shared by both diseases which may seriously confound the diagnosis

Description of pain The common terms used to describe the pain of esophagitis are heartburn warmth fullness pressure distress gnawing a lump—terms quite indistinguishable from those used to describe angina pectoris Among these perhaps the most common is *heartburn* or its equivalent When this term is used it is helpful to ask whether the burning sensation more closely resembles *heat* or *acid* The latter response is quite characteristic of esophagitis but is almost never used to describe ischemic heart pain Symptoms of esophagitis generally occur after eating and are often initiated or aggravated by recumbency While this sequence is not particularly common in patients with angina pectoris is it important to remember that with rare exceptions patients with ischemic heart pain too avoid lying flat when they have pain

The distribution of esophageal pain is quite similar to that of angina pectoris Most often it is midline thoracic or abdominal (from the suprasternal notch to the epigastrium) but may extend to the left or right chest the shoulders, arms and hands the back or throat In one series of ninety six patients discomfort was substernal in 70 per cent, abdominal in 67 per cent and radiated to the neck arms or back in 19 per cent of patients [19] Although exertional pain has been reported in some patients with esophagitis,[20,21] the possibility of coexisting coronary heart disease in these patients has not been completely excluded

Esophageal pain simulating ischemic heart pain may also be the consequence of diffuse esophageal spasm or less often achalasia In a group of 43 patients with chest pain and either normal coronary angiograms or negative exercise tolerance tests esophageal manometrics revealed high amplitude non peristaltic contractions in one third of the patients [22] Diffuse esophageal spasm is generally initiated by swallowing particularly of cold liquids and increased sensitivity to cholinergic drugs and endogenous gastrin may play a role in precipitating symptoms [23] A favorable response to nitrates in subjects with diffuse esophageal spasm further confounds the problem of distinguishing this condition from angina pectoris [24, 25]

Summary Since both esophagitis and coronary heart disease are common conditions it is expected that the two diseases will frequently coexist Indeed the demonstration that one or both conditions are present does not establish with certainty the cause of a given pain syndrome While endoscopy may indicate that esophagitis is present a positive esophageal acid perfusion test provides further evidence that esophageal erosion is the source of pain [19] Similarly chest pain and dysphagia precipitated by swallowing cold liquids and associated with high amplitude non peristaltic esophageal contractions strongly suggest that diffuse esophageal spasm is responsible for the symptoms [22] In the presence of both coronary and esophageal disease provocative tests may be necessary to ascertain the origin of an atypical chest pain syndrome

Radicular syndromes The pain of spinal particularly cervical root compression does not frequently mimic ischemic heart pain Nontheless in some instances an effort syndrome virtually indistinguishable from angina pectoris may b

due to thoracic or lower cervical nerve root compression Generally however historical features or provocative maneuvers on physical examination will lead to a correct diagnosis

Description of pain *Dorsal* root pain is generally sharp and piercing often of lightning character and may be associated with superficial paresthesias On the other hand *ventral* root pain may be a deep boring dull discomfort simulating ischemic heart pain Spinal pain may occur over any part of the chest the paraspinal area the axilla or shoulder girdle and may radiate down the inner or outer aspect of the arm to the fingers Generally it is bilateral but the symptoms from one side of the body most often dominate

The three major characteristics of root pain are (1) pain with movement of the body (2) pain on coughing sneezing etc (Déjerine s sign) and (3) pain after prolonged recumbency[26] Shoulder or arm pain may be brought on by rotation of the head to the involved side or flexion of the head to the uninvolved side Chest pain is often precipitated by bending hyperextension of the upper spine or by throwing back the shoulders Déjerine s sign is most apt to be observed when the condition is acute Indeed the onset of symptoms may be traced for example to a particularly vigorous sneeze The development of root pain after several hours in bed is a common feature of this syndrome and thus may be misinterpreted as nocturnal angina particularly when associated with other constitutional symptoms (vide infra)

Repeated jarring such as occurs with running jogging driving on a bumpy road jumping rope etc will often provoke root pain and thus exhibit characteristics which may closely resemble angina pectoris Recently a syndrome designated cervicoprecordial angina has been described which consists of substernal chest pain simulating angina pectoris but due to cervical root compression[27] Exercise induced pain was present in 14 of 17 patients and 12 obtained prompt relief of symptoms with nitroglycerin Chest pain was reproduced by a number of provocative maneuvers (vide infra) and all patients had normal coronary arteriograms The pain was substernal radiating to the arms and fingers in most patients and usually lasted less than 15 minutes Relief of symptoms was obtained in the majority of patients by using cervical traction and a six week course of phenylbutazone although in some patients laminectomy and foraminotomy were necessary for successful treatment

Associated symptoms Paresthesias are common and occasionally precede the onset of root pain Tingling numbness and stiffness particularly of the fingers are generally aggravated by the same maneuvers which provoke pain Vertigo is not infrequently associated with upper cervical root compression and may be accompanied by nausea Difficulty in breathing without hyperpnea has been reported in one third of patients with chest pain due to cervical root compression[26] further suggesting a cardiac origin of these symptoms In rare instances this peculiar respiratory distress may be the only manifestation of the disease

Physical examination The diagnosis of spinal root compression is established by a series of provocative maneuvers Stretching the arm across the chest while pulling the head toward the flexed shoulder and inhaling deeply is one such maneuver Pressure applied to the top of the head with the head tilted slightly to one side or the other (Spurling s compression maneuver) is another Tenderness to deep palpation is an extremely valuable sign In Davis series[6] of 100 patients with chest pain of root origin moderate or marked spinal tenderness was present in 94% and parasternal or axillary tenderness was present in 98% of those with thoracic root compression[2] In one third of patients firm pressure over the spinous processes evoked referred pain over the anterior or lateral chest wall Hyperesthesia or hypesthesia to pin prick or light touch may be present Maneuvers used to identify the thoracic outlet syndromes are also important the Adson maneuver for the scalenus anticus syndrome (obliteration of the arterial pulse during inspiration while the chin is elevated and rotated to the affected side) the chicken ready to fly sign (abduction and rotation of the upper arms) for the costoclavicular syndrome and the hyperabduction maneuver for the pectoralis minor and humeral head syndromes.

Summary Chest pain produced by spinal root compression may on occasion be deep boring constricting short lived evoked by physical exercise and relieved by rest and even nitroglycerin Since symptoms of vertigo nausea and respiratory distress may accompany radicular pain distinction between spinal root pain and angina

V., and Gorlin R Dia tolic heart sounds and filling waves in coronary heart disease Circulation 44 196 1971
8. Cohn P F Gorlin R., Vokonas, P S., Williams, R A., and Herman M V A quantitative clinical index for the diagnosis of symptomatic coronary artery disease N Engl J Med 286:901 1972.
9 Weiner D A., Ryan T J., McCabe C H., Kennedy J W Schloss, M., Tristani, F Chaitman B R., and Fisher L. D Correlations among history of angina ST segment response and prevalence of coronary artery disease in the coronary artery disease surgery study N Engl J Med 301 230 1979
10 Borer J S., Kent, K. M., Bacharach S L. Green M V., Rosing D R., Seides, S F., Epstein S E., and John ton G S Sen itivity pecificity and predictive accuracy of radionuclide cineangiography during exercise in patients with coronary artery disease Comparison with exercise electrocardiography Circulation 60 572 1979
11 McCarthy D M., Blood D K. Sciacca R R., and Cannon P J Single dose myocardial perfu ion imaging with Thallium 201 application in patients with non diagnostic electrocardiographic stress tests, Am J Cardiol 43 899 1979
12. Jeresaty R. M Mitral valve prolapse New York, 1979 Raven Press.
13 Abinader E G Adrenergic beta blockade and ECG changes in the systolic click murmur syndrome, AM HEART J 91 297 1976.
14 Friesinger G C., Biern R. D Likar I., and Mason R E. Exercise electrocardiography and vasoregulatory abnormality Am J Cardiol 30 733 1972.
15 Behar S., and Kariv I Effect of propranolol on "non ischemic" ST segment and T wave changes Differentia tion of coronary from non-coronary ECG changes, Chest 63 376 1973
16. Tresh D D., Soin J S., Siegel, R., Love M., and Keelan M H., Jr Mitral valve prolapse—evidence for a myocar dial perfu ion abnormality Am J Cardiol 41 441 1978
17 Braunwald F., Lambrew C T., Rockoff S D., Ross, J., Jr., and Morrow W G Idiopathic hypertrophic subaor tic tenosi 1 A description of the disease based upon an anal is of 64 patients Circulation 30 IV 3 1964
18 Criley J M., Lennon P A., Abbasi, A. S and Blaufus A. H Hypertrophic cardiomyopathy in Clinical Cardio-vascular Physiology H J Levine ed., New York 1976 Grune & Stratton, Inc pp 771-8_7
19 Bernstein J M Fruin R C and Pacini R Differen tiation of esopha eal pain from angina pectoris Role of the esophageal acid perfusion test Medicine 41 143 1962
20 Jones C M Hiatu esophageal hernia with pecial reference to comparison of it symptom with those of angina pectoris N Engl J Med 225 963 1941
21 McHardy G M Hardy R J and Craighead C C Erosive esophagitis Ga troenterology 34 760 1958
22. Brand D L. Martin D., and Pope C E., II Esoph manometrics in patients with angina like chest pain J Dig Dis 22 300 1977
23 Cohen S Motor disorders of the esophagus, N Engl Med 301 184 1979
24 Orlando R C and Bozym ki, E M. Clinical manometric effects of nitroglycerin in diffuse esoph pa m N Engl J Med. 289 23, 19 3
25 Swamy N Esophageal spa m clinical and man response to nitroglycerin and lon actin ni n es, Ga troenterology 72 23 1977
26 Davis, D., Radicular Syndrome With Emphasis Chest Pain Simulating Coronary Disease Chicago, 19 Year Book Medical Publishers, Inc
27 Myers, G., Freeman R Herz D., and Sta , Cervicoprecordial angina diagnosis and man Am. J Cardiol. 39 287 1977
28 Likoff W., Segal, B L., and Kasparian, H Paradox normal selective coronary arteriogram in pa ients c sidered to have unmistakable coronary heart disease Engl. J Med 276 1063 1967
29 Kemp H G., Elliot W C., and Gorlin R. The syndrome with normal coronary arteriography Tr Assoc. Am Physicians 80 59 1967
30 Kemp H G., Vokonas P S., Cohn. P F., and Gorlin The anginal syndrome associated with normal coron arteriograms Report of ix years experience Am Med 54 735 1973
31 Bemiller C R Pepine C J and Rogers, A. R Lo term observations in patient with angina and n coronary arteriograms, Circulation 47 36 19 3
32 Neill, W A., Kassenbaum, D G and Judkins, M Myocardial hypoxia as the basis for angina pectoris patient with normal coronary arteriograms, N E Med 279 789 1968
33 Jacobs, W F., Battle W E and Ronan, J A., False positive ST T wave changes secondary to hy ventilation and exercise Ann. Intern. Med. 81 1974
34 Lary D., and Goldschlager N Electrocardio changes during hyperventilation resembling myocard ischemia in patients with normal coronary arteriogr AM HEART J 87 383 1974
35 Prinzmetal M., Kennamer R., Merlis, R., Wada T Bor N Angina pectoris I a variant form of a pectoris Am J Med. 27 375 19 9
36. Levine S A., and Ernsteno A C Observations arterial blood pressure during attack of angina pect AM HEART J 8 323 1933
37 Gaasch, W H Exercise testing in variant angina Ch 74 612 1978
38 Wehrmacher W H The painful anterior chest syndromes, Med Clin North Am. 42 111 19

tension are not infrequent during episodes of variant angina. The underlying mechanism responsible for this clinical syndrome is coronary artery spasm. Nonetheless, the majority of patients with variant angina also have fixed coronary arterial lesions with a high incidence of single vessel disease. Despite generally good exercise tolerance, an abnormal exercise ECG is not unusual in patients with variant angina[37] and thus it is of limited value in distinguishing typical and variant angina. Nitrates are extremely effective in relieving ischemic pain due to coronary spasm. On the other hand, beta adrenergic blocking agents may aggravate symptoms. Hence a paradoxical response to propranolol therapy should alert the physician to consider the diagnosis of variant angina.

Chest wall syndromes. Chest pain of musculoskeletal origin is often dull and aching but at times may be sharp or stabbing, particularly when the involved portion of the thorax is moved. Regardless, the character of the pain may be embellished by fear of a cardiac origin giving rise to hyperventilation, palpitations, or a visceral discomfort superimposed upon the primary musculoskeletal pain. With rare exceptions the diagnosis is easily established by a careful physical examination. Tietze's syndrome, for example, is an uncommon condition consisting of painful, tender, and swollen costochondral or sternoclavicular junctions sometimes initiated by excessive strain on the rib cage.[3] The upper ribs are most commonly affected, and pain is frequently aggravated by respiratory straining, weather changes, and perhaps by anxiety. Since physical activity may trigger chest wall pain, the symptoms may be misinterpreted as angina pectoris. Although the course may be prolonged, symptoms are generally easily controlled by reassurance, heat, salicylates, or if necessary by local injections of xylocaine or steroids. Costochondrodynia is far more common than Tietze's syndrome and differs in that there is no swelling of the involved, tender costochondral junction. In these and most other painful chest wall syndromes, the key to the diagnosis is localized tenderness in the painful area or referred chest pain with localized pressure to a portion of the chest wall.[3]

Pericarditis. Ordinarily there is little difficulty distinguishing the pain of pericarditis from that of myocardial ischemia. The pleuritic component is identified by deep breathing, sniffing, or by any abrupt motion of the diaphragm or pleural surface. Rarely, however, acute pericarditis will present with an oppressive, steady chest pain and constitutional symptoms identical to that of patients with myocardial ischemia or infarction. Serum elevations of creatine kinase MB isoenzyme and acute repolarization changes on the electrocardiogram may mislead the physician to favor a diagnosis of infarction. Careful attention to antecedent symptoms of a viral infection, inappropriate fever, failure of the elevated ST segments to evolve a pattern of transmural or non transmural infarction, a negative "hot spot" scan, etc., may be necessary to establish that the process is one of epicardial injury rather than coronary vascular disease. Repeated auscultation for a pericardial friction rub and an echocardiographic search for pericardial fluid will help to resolve the issue.

There are many other medical emergencies which may simulate acute coronary heart disease. Pulmonary embolism, aortic dissection, acute pancreatitis, spontaneous mediastinal emphysema, pneumonia—all may be confused with acute myocardial infarction. In these circumstances, however, the presentation is generally a sudden single event. The response of the physician to these acute situations must be immediate with a priority of diagnostic procedures based upon those treatable diseases which represent a threat of life. On the other hand, the approach to recurrent chest pain syndromes should be more contemplative with a special effort made to detect less serious alternatives to chronic coronary heart disease.

REFERENCES

1. Winsor T: Pain and autonomic responses in acute myocardial infarction, *in* Coronary Heart Disease, W. Likoff and J. H. Moyer, eds., New York, 1963, Grune & Stratton, Inc., pp. 235.
2. Mudge G. H., Grossman W., Mills, R. M., Lesch, M., and Braunwald, E.: Reflex increase in coronary vascular resistance in patients with ischemic heart disease. N. Engl. J. Med. 295:1333, 1976.
3. Longhurst, J. C., and Ashton, J. H.: Canine cardiovascular reflexes resulting from capsaicin stimulated gastric receptors (Abst.). Circulation 58 II 9, 1978.
4. Gorlin, R.: Coronary Artery Disease. Philadelphia, 1976, W. B. Saunders, Company, pp. 150-185.
5. Lown, B., and Levine, S. A.: The carotid sinus. Clinical value of its stimulation. Circulation 23:766, 1961.
6. Levine, H. J., McIntyre, K. M., and Glovsky, M. M.: Relief of angina pectoris by Valsalva maneuver. N. Engl. J. Med. 275:487, 1966.
7. Cohn, P. F., Vokonas, P. S., Williams, R. A., Herman, M.

I Electrophysiology of atropine

a Sinus node and the atrial muscle

1 Sinus node automaticity The administration of atropine is a dose of 0 5 mg or more usually accelerates the sinus rate by direct parasympathetic blockade In addition to this positive chronotropic action atropine given in small doses intravenously can slow the sinus rate or less frequently, may produce a biphasic effect [3 6 43] The biphasic effect of atropine can also be seen immediately after a higher dose or even following intramuscular administration [44] A biphasic response is characterized by initial slowing of the heart rate which is usually followed within 2 to 3 minutes by a positive chronotropic effect The mechanism underlying the slowing effect of atropine is unclear Das and colleagues[43] believe that in addition to producing sinus bradycardia by a central action low doses of atropine inhibit cholinesterase or may influence the activity of the peripheral sympathic nervous system

The effects of atropine on sinus bradycardia and other manifestations of sinus node dysfunction have also attracted attention recently The response to atropine is variable In some patients atropine adequately increases the heart rate whereas in others the response to this drug is barely measurable This effect of atropine most likely depends on the cause of sinus bradycardia itself In other words a minimal response to atropine may be related to intrinsic disease of the SA node while a more satisfactory response *suggests an extracardiac origin or so called phys*iologic bradycardia [47] The usefulness of atropine in the evaluation of sinus node dysfunction will be discussed in more detail below

Automaticity of the SA node can also be evaluated by measuring the sinus node recovery time (SNRT) which is the duration of atrial asystole after rapid atrial pacing is discontinued It is believed *that this method is more sensitive* than pharmacologic tests in the differentiation of intrinsic sinus node dysfunction from physiological bradycardia The pause in atrial activity after discontinuation of rapid atrial pacing is mainly a measure of the functional status of the SA node and is longer in patients with decreased SA node automaticity than in those with normally functioning sinus node According to some authorities however the effect of rapid atrial pacing is more complex than simple inhibition of the automaticity of the SA node and the sensitivity *of this test for sinus node* dysfunction is low [3 47 4]

In general, atropine shortens the SNRT in normal individuals and in most patients with sinus node dysfunction [2 30 3 14] Atropine paradoxically prolongs the SNRT or produces a transient AV junctional rhythm when given to some patients with sinus node dysfunction [5 31] This paradoxical effect on *SNRT* may be mediated through the effect of atropine in improving sinoatrial conduction Because the number of impulses entering the SA node after atropine is greater the SA node itself will be suppressed Reiffel et al[1] suggested that this paradoxical effect of atropine on the SA node could also result from concealed conduction or from altered conduction within the SA node

2 Sinoatrial conduction Impaired automaticity of the SA node is only one function which can underlie sinus node disease Strauss and co workers [8] have suggested that another abnormality impaired sinoatrial conduction (SAC) may be involved This assumption has not been accepted by all For instance Scherf[5] and Dighton believe that SA block is a manifest*ation of* SA nodal disease rather than of true conduction defect On the other hand electrophysiological observations and experimental studies by Strauss and Bigger[54] point to the existence of true sinoatrial block

Sinoatrial conduction time can now be measured only indirectly using artificial atrial premature stimulation[48] or in *patients with* atrial parasystole as described by Langendorf and colleagues [55] By this method [48] the sinoatrial conduction time is calculated to be the difference between the basic cycle and the return cycle following introduction of an artificial atrial premature beat According to this concept antegrade and retrograde conduction between the SA *node and the atria are the* same and the artificial impulse only resets the SA node and has no influence on its automaticity

The effect of atropine on sinoatrial conduction time has also been studied by several groups of workers Among them Bissett and co workers and others [5 57 58] demonstrated a shortening of the sinoatrial conduction time after the administration of atropine to subjects with normal SA node function while Reiffel and Bigger[54] also showed improved sinoatrial conduction time in patients with sinus bradycardia On the other

The effect of atropine on cardiac arrhythmias and conduction Part 1

Paul Schweitzer M D F A C C
Herbert Mark M D F A C C
Bronx N Y

The effects of atropine on cardiac rhythm have been known since 1912 when Robinson and Draper[1] abolished atrial premature beats with the drug and 1915 when Wilson induced atrioventricular (A V) dissociation These results established a pattern of investigation for early workers who then concerned themselves with the effects of atropine on A V conduction More recently since the report of Agress and Binder the effectiveness of atropine in acute myocardial infarction complicated by bradycardia was investigated intensively In subsequent studies with atropine Thomas and Woodgate and Harris and Bluestone using atropine corrected both bradycardia and hypotension occurring in patients with myocardial infarction and in a more extensive series of patients Adgey and colleagues found that atropine corrected bradycardia and hemodynamic abnormalities and also suppressed ventricular premature beats As a result this clinical setting became the prime indication for atropine

Following introduction of intracavitary electrocardiography and pacing techniques the usefulness of atropine in the management of patients with sinus node dysfunction was assessed and its effect on the electrophysiological functions of the sinoatrial (SA) and atrioventricular (AV) nodes was analyzed

The number of studies reported increased and inevitably some confusion about the usefulness of atropine also arose as some studies led to apparently conflicting data and note was made of hazards arising from atropine s use

Accordingly in this review we will summarize the electrophysiological effect of atropine on the cardiac conduction system and myocardium and attempt to establish criteria and guidelines for its use and explain some of its seemingly conflicting and paradoxical effects

Best known of the cardiac effects of atropine is its ability to increase heart rate and facilitate A V conduction by its vagolytic action on the sinus node However atropine also exerts direct influence on the function of the AV junctional tissue and the subjunctional components of the specialized conducting system Some of the other effects of atropine are indirect and are probably related to unopposed action of the sympathetic nervous system or simply to an increased heart rate The response to atropine also depends on the varying sensitivity of different levels of the specialized conducting system to autonomic stimuli In fact under circumstances to be described not all components of the specialized conducting system will respond to vagal stimulation or blockade Furthermore the differing sensitivity to atropine of the various structures of the specialized conducting system may lead to unpredictable and apparently paradoxical effects

The amount of atropine necessary to produce complete blockade of the parasympathetic nervous system is uncertain According to some workers 2 0 mg of atropine should inhibit the vagus nerve while Jose and Chamberlain and co workers believe that as much as 3 to 6 mg of atropine is needed to block the vagus completely

From the Cardiology Section Department of Medicine Bronx Veterans Administration Medical Center Mount Sinai School of Medicine New York N Y and Jersey City Medical Center Jersey City and New Jersey Medical School Newark N J

Received for publication Feb 20 1980

Reprint requests Paul Schweitzer M D Cardiology Section Bronx V A Medical Center 130 West Kingsbridge Rd Bronx N Y 10468

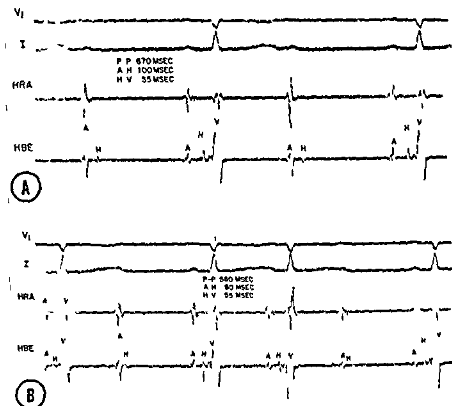


Fig 2 (Patient 2) The effect of atropine on second degree AV block *From the top to bottom* Lead V_1 I high right atrial electrogram *(HRA)* and His bundle electrogram *(HBF)* *A* there is a 2 1 AV block Each atrial deflection is followed by an H spike confirming the presence of a block below the AV node *B* five minutes after the administration of 1 0 mg of atropine the 2 1 AV block changed to 3 2 AV block

the pacemaker localized in the distal part of the His bundle can also respond to autonomic stimuli[62, 64]

2 *Atrioventricular conduction* Facilitation of AV nodal conduction by atropine in patients with normal AV nodal conduction is a well known effect Akhtar and colleagues[37] and others[38] demonstrated that atropine improves AV nodal conduction and decreases both the effective and functional refractory period of the AV node Further second degree AV block is achieved at higher pacing rates after the administration of atropine Shortening of AV nodal conduction time is manifested regardless of the dose of the drug administered[4]

The effects of atropine on first degree AV block from different causes are variable and unpredictable[4, 7] In second degree AV block the response to atropine is more consistent In general type one second degree AV block will disappear after the administration of atropine while the drug tends to be ineffective in type two second degree AV block[65, 7]

Dual AV nodal pathway (DAVNP) is a not uncommon condition characterized by the presence of two intranodal pathways with different refractoriness and conductivity[68] One pathway which conducts the atrial impulse faster usually has a longer effective refractory period whereas the second pathway through which the impulse travels more slowly tends to have a shorter effective refractory period Neuss and co workers[69] studying the effect of atropine in eight patients with DAVNP abolished the DAVNP in four while in three patients the drug was ineffective and in one case DAVNP was unmasked by atropine Recently Akhtar and co workers reported five patients in whom neither atrial pacing nor atrial extrastimulation induced paroxysm of supraventricular tachycardia at rest while following administration of atropine atrial premature beats initiated a supraventricular tachycardia It is likely that in this study atropine unmasked a DAVNP which is now assumed to be a necessary electrophysiological abnormality for initiation of a reentrant tachycardia[11]

c His Purkinje system and ventricular muscle

1 *Automaticity of the His Purkinje system* A influence of the parasympathetic nervous syste

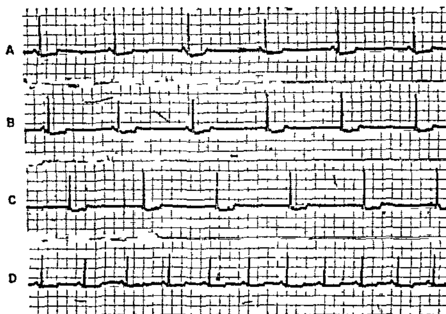


Fig 1 (Patient 1) Atropine-induced AV junctional rhythm *A* sinus bradycardia with a rate of 37/minute *B* and *C* two minutes after the administration of 1 0 mg of atropine there is an AV junctional rhythm and AV dissociation *D* sinus rhythm at a rate of 74/minute resumes five minutes after the administration of atropine

hand Dhingra and associates[57] found that while atropine shortens sinoatrial conduction time in normal patients it does not have this effect in the presence of sinus node dysfunction

3 Atrial muscle Reports of the effect of atropine on the refractoriness of atrial muscle in man are few and also conflicting Some authors[7] found shortening of the effective refractory period of the atrial muscle in normal individuals after atropine but others have not been able to confirm these findings[37] [8] nor does atropine significantly influence the effective refractory period of the atrial muscle in patients with sinus node dysfunction according to Dhingra and co workers[5]

b Atrioventricular junction

1 Atrioventricular junctional pacemaker Atropine stimulates the atrioventricular junction pacemaker in normal patients and in those with sinus nodal disease In normal subjects the increased activity of the AV junctional pacemaker becomes evident immediately after the administration of atropine when the drug temporarily suppresses the SA node and stimulates the subsidiary pacemaker

This effect is demonstrated by the following patient A 72 year old man was admitted because of syncope The ECG on admission showed sinus bradycardia with a rate of 37/minute (Fig 1*A*) Two minutes after the administration of 1 0 mg of atropine there was a slight decrease of sinus rate after which AV dissociation appeared (Fig 1*B* and *C*) Five minutes following the administration of atropine the sinus rhythm increased to 74/minute (Fig 1*D*) and the AV dissociation was abolished

In some patients with sinus node dysfunction the resulting AV junctional rhythm can last for as long as 3 hours The mechanism for this sustained AV junctional rhythm is not well understood We suggest that in these patients the SA node becomes unresponsive to automatic stimuli, permitting the effect of atropine on the AV junctional pacemaker to become dominant

Atropine may also be useful in helping to localize the level of the block in patients with complete AV block and narrow QRS complexes Narula and associates[59] studying the effect of atropine in 11 patients with these electrocardiographic features noted that atropine increased the rate of the escape pacemaker in five patients and had no effect on the subsidiary pacemaker in the remaining six They postulated that in patients who responded to atropine the subsidiary pacemaker was in the AV junction while the nonresponder had the escape pacemaker within the His bundle These results have been confirmed[6] [61] but recent case reports suggest that

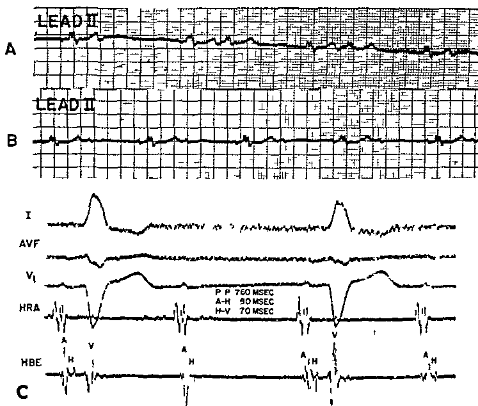


Fig 4 (Patient 3) The effect of atropine on second degree AV block *A* atrial bigeminy the atrial beat after the first and fourth beat is blocked *B* administration of 1 0 mg of atropine suppresses the atrial premature beats and produces a 2 1 AV block *C from top to bottom* Lead I aVF V high right atrial electrogram *(HRA)* and His bundle electrogram *(HBE)* 2 1 AV block localized below the AV node is demonstrated

with shortening of the A H interval (Fig 2*B*) After an acute inflammatory or ischemic disease had been ruled out by appropriate study the patient underwent exercise testing The resting ECG showed 3 2 AV block (Fig 3*A*) During exercise there were short episodes of 1 1 conduction despite a rapid sinus rate (Fig 3*B* *C* and *D*)

Finally atropine also has a paradoxical effect on AV conduction by causing AV block or increasing a pre existing conduction abnormality Most patients responding in this manner had conduction defects below the AV node [7] or acute myocardial infarction The apparent paradoxical effect of atropine in patients with subnodal conduction defect probably results from an increased sinus rate which unmasks the conduction abnormality below the AV node

Our third case illustrates this effect of atropine The patient is an 82 year old man seen in the emergency room because of dizziness The ECG showed sinus rhythm with the rate of [illegible] minute and frequent atrial premature beats some of them blocked A rhythm strip (Fig 4*A*) shows atrial bigeminy Administration of 1 0 mg of atropine increased the sinus rate to 83/minute suppressed the atrial irritability and initiated a 2 1 AV block (Fig 4*B*) Thirty minutes after the development of the AV block a His bundle electrogram was recorded (Fig 4*C*) The intracavitary recording demonstrated the conduction defect below the AV node Atropine not only suppressed the APC s but also uncovered an AV conduction disturbance

Worsening of AV conduction or development of paroxysmal AV block in patients with acute myocardial infarction after the administration of atropine has been reported [77, 78] The localization of AV block caused by atropine in these patients was not confirmed by His bundle recording and therefore we do not know at what level the AV conduction was impaired Because some of these reported patients had inferior myocardial infarction in which the block is usually localized in the AV node it is assumed that atropine caused a conduction disturbance within the AV node

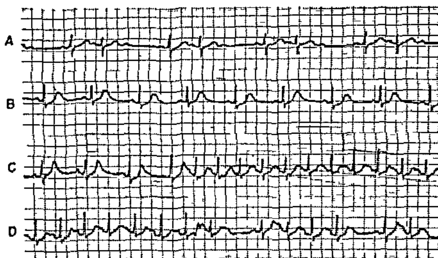


Fig 3 (Patient 2) The effect of exercise on second-degree AV block Lead V *A* resting ECG shows 3 2 AV block with an atrial rate of 93/minute *B* during exercise the atrial rate increases to 135/minute and the AV block changes from 3 2 to 2 1 *C* and *D* transient 1 1 conduction is noted at the same atrial rate as in *B*

on the automaticity of the His Purkinje system was postulated in patients with advanced AV block and idioventricular rhythm by Schwartz and de Sola Pool[8] who demonstrated that atropine increases the idioventricular rate and also suppresses ventricular irritability in patients with third degree AV block Following a renewal of interest in this problem recent studies suggested that the subnodal portion of the His Purkinje conducting system is indeed under parasympathetic influence Bailey and co workers[72] showed that in in vitro preparations acetylcholine decreased phase four diastolic depolarization in the proximal part of the intraventricular conducting system Danilo and associates[73] demonstrated the same effect on the Purkinje system and also showed that atropine blocks the effect of acetylcholine on the intraventricular conducting system

Existence of parasympathetic innervation of the subjunctional specialized conducting system was also confirmed by Kent and co workers[74] The response of the intraventricular conducting system to parasympathetic stimulation is further supported by Waxman and Wald [5] who were able to interrupt ventricular tachycardia in humans by vagal stimulation Finally the previously discussed response of the subjunctional pacemakers to autonomic stimuli is consistent with these experimental findings [64] On the other hand Narula and colleagues and others [6 6] believe that the subjunctional pacemakers are insensitive to vagal stimulation

2 *His Purkinje system conduction* The effect of atropine on subjunctional conduction is also unclear It is generally believed that a conduction disturbance below the AV node will not improve or may even be aggravated after the administration of atropine [65 6]

Patients with conduction disturbance within the His bundle are the most suitable group in which to test the effect of atropine on subnodal conduction According to Gupta and colleagues [7] there are patients with intra Hisian block in whom atropine improves conduction but the response to atropine of the subjunctional conducting system is less predictable The reason for this variable effect of atropine on the conduction through the His bundle is unclear One can speculate that the response to atropine depends on the site of conduction defect within the His bundle That is to say atropine is more effective in a proximal than in a distal intra Hisian block [76]

The effect of atropine on AV conduction in our next patient supports our contention that there are important subjunctional parasympathetic effects The patient is a 46 year old man with a history of dizziness of one day duration The electrocardiogram on admission showed 2 1 AV block Subsequently a His bundle electrogram was recorded before and after 0 1 mg of atropine following which a temporary pacemaker was inserted into the right ventricle The His bundle recording demonstrated a block below the AV node (Fig 2A) Administration of atropine increased the heart rate from 89/minute to 107/minute and the block changed from 2 1 to 3 2

in man after the administration of atropine Arch Intern Med 16 989 1915
3 McGuigan H The effect of small doses of atropine on the heart rate J A M A 76 1338 1920
4 Rudolf R D and Bulmer F M R Some cardiac effects of atropine Am J Med Sci 168 641 1924
5 Nefelski L A and Brown C F G Action of atropine on the cardiovascular system in normal persons Arch Intern Med 86 898 1950
6 Bruenn H G The mechanism of impaired auriculoventricular conduction in acute rheumatic fever Am Heart J 13 413 1937
7 Robinson R W Effect of atropine upon the prolongation of the PR interval found in acute rheumatic fever and certain vagotonic persons Am Heart J 29 378 1945
8 Schwartz S P and de Sola Pool N Transient ventricular fibrillation III The effect of bodily rest atropine sulfate and exercise on patients with transient ventricular fibrillation during established auriculoventricular dissociation A study of the influence of the extrinsic nerves on the idioventricular pacemaker of the heart Am Heart J 39 361 1950
9 Averil H and Lamb E Less commonly recognized action of atropine on cardiac rhythm Am J Med Sci 237 304 1959
10 Gravenstein J S Ariet M and Thonby J I Atropine on the electrocardiogram Clin Pharmacol Ther 10 660 1969
11 Kottmeier C A and Gravenstein J S The parasympathomimetic activity of atropine and atropine methyl bromide Anesthesiology 29 1125 1968
12 Agress C M and Binder M J Cardiogenic shock Am Heart J 54 458 1957
13 Thomas M and Woodgate D The effect of atropine on bradycardia and hypotension in acute myocardial infarction Br Heart J 28 409 1966
14 Harris A and Bluestone R Treatment of slow heart rate following acute myocardial infarction Br Heart J 28 631 1966
15 Adgey A A J Geddes J A Mulholland H C Keegan D A J and Pantridge J F Incidence significance and management of early bradyarrhythmia complicating acute myocardial infarction Lancet 2 1097 1968
16 Lown B, Klein M D and Hershberg I I Coronary and precoronary care Am J Med 46 705 1969
17 Shillingford J and Thomas M Treatment of brady cardia and hypotension syndrome in patients with acute myocardial infarction Am Heart J 75 843 1968
18 Gregory J J and Grace W J The management of sinus bradycardia nodal rhythm and heart block for the prevention of cardiac arrest in acute myocardial infarction Progr Cardiovasc Dis 10 0 1968
19 Rotman M Wagner G S and Wallace A G Bradyarrhythmia in acute myocardial infarction Circulation 45 703 19
20 Webb S W Adgey A A J and Pantridge J F Automatic disturbance at the onset of acute myocardial infarction Br Med J 3 8 1
21 Grauer L E Gershein B J Orland M M and Epstein S E Bradyarrhythmia and its complications in the prehospital phase of myocardial infarction Am J Cardiol 32 607 1973
22 Stock E Prophylactic total coronary care Am Heart J 85 814 1973
23 Scheinman M M Thorburn D and Abbott J A Use of atropine in patients with acute myocardial infarction and sinus bradycardia Circulation 52 6
24 Chadda K D Lichstein E Gupta P K and Choy R Bradycardia hypotension syndrome in acute myocardial infarction Am J Med 59 158 1975
25 Kounis N G and Chopra R K Atropine and bradycardia after myocardial infarction Ann Intern M 81 117 1974
26 Chadda K D Lichstein E Gupta P K and Kou e sis P Effects of atropine in patients with bradyarrhythmia complicating myocardial infarction Usefulness of an optimum dose for overdrive Am J Med 63 503 197
27 Warren J V and Lewis R P Beneficial effects of atropine in prehospital phase of coronary care Am J Cardiol 37 68 1976
28 Rosen K M Loeb H S Ziad Sinno M Rahimtoola S H and Gunnar R M Cardiac conduction in patients with symptomatic sinus node disease Circulation 43 8 1971
29 Mandel W Hayakawa H Danzing R and Marcus H S Evaluation of sinoatrial node function in man by overdrive suppression Circulation 44 59 1971
30 Narula O S Samet P and Javier R P Significance of sinus node recovery time Circulation 45 140 1972
31 Lloyd Mostyn R H and Oram S Sinoatrial disorders including the bradycardia tachycardia syndrome Q Med 42 41 1973
32 Mandel W Havakawa H Allen H N and Kerma A I Assessment of sinus node function in patients with sick sinus syndrome Circulation 46 761 1972
33 Boudoulas H Engel T R and Schaal S F The effect of pharmacologic agents and atrial pacing on ... function and atrioventricular conduction (Abstract) Circulation 46(Suppl) II 39 1972
34 Ries J C Bashour T and Cheng T O Atrial pacing in sick sinus node syndrome (Abstract) Circulation 46(Suppl II) 211 1972
35 Gupta P K Lichstein E Chadda K D and Badui E Appraisal of sinus nodal recovery time in patients with sick sinus syndrome Am J Cardiol 34 265 1974
36 Reiffel J A and Bigger J T The effect of atropine on sinus node function in adults with sinus bradycardia (Abstract) Am J Cardiol 35 165 1975
37 Akhtar M Damato A N Caracta A R Batsford W P Josephson M E and Lau S H Electrophysiologic cal effect of atropine on atrioventricular conduction studied by His bundle electrogram Am J Cardiol 33 333 1974
38 Bissett J K DeSovza N B Kane J J and Murphy M L Electrophysiology of atropine Cardiovasc Res 9 73 1975
39 Jones R E Deutsch S and Turndorf H Effect of atropine on cardiac rhythm in conscious and anesthetized man Anesthesiology 22 67 1961
40 Kahler R L Gaffney T E and Braunwald E The effect of autonomic nervous system inhibition on the circulatory response to muscular exercise J Clin Invest 41 198 1962
41 Jose A D The effect of combined sympathetic and parasympathetic blockade on heart rate and cardiac function in man Am J Cardiol 18 4 6 196
42 Chamberlain D A Turner P and Sneddon J M Effects of atropine on heart rate in healthy man Lancet 2 12 196
43 Da C Talmers F N and Weisler A M New Observations of the effects of atropine on the sinoatrial and atrioventricular nodes in man Am J Cardiol 36 281 19
44 Hayes A H Copelan H W and Ketchum J Effects of large intramuscular doses of atropine on

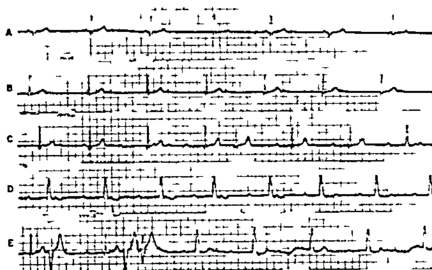


Fig 5 (Patient 4) The effect of atropine on the sinus node and AV conduction in a patient with inferior myocardial infarction Lead I *A* before administration of atropine there is sinus bradycardia at a rate of 36/minute and sinoatrial block The fourth and seventh beats are AV junctional escape beats *B* the sinus bradycardia is replaced by AV junctional rhythm at a rate of 36/minute after the administration of 1.0 mg of atropine *C* the AV junctional rhythm lasted for one minute after which sinus rhythm complicated by high grade AV block appeared Only the fifth sinus impulse is conducted into the ventricle The ventricles were controlled by an AV junctional pacemaker *D* the AV block persisted and the QRS complex become wide measuring 0 11 sec The rates of the narrow and wide QRS complexes were the same (38/minute) *E* the first two narrow QRS complexes precede ventricular premature beats. Elsewhere the QRS complexes are wide From *C* to *E* there is a progressive increase of the atrial rate from 60/minute to 100/minute

However this assumption requires confirmation because the situation is probably more complex and atropine may unmask impairment of conduction at more than one level as is indicated by our fourth patient

The patient a 42 year old man was admitted with an acute inferior myocardial infarction On the tenth day in the hospital after an uncomplicated initial course the patient developed syncope An ECG taken at that time showed sinus bradycardia with a ventricular rate of 36/minute sinoatrial block and AV junctional escape beats (Fig 5*A*) Atropine in a dose of 0 5 mg was ineffective and therefore a second dose of 0 5 mg of atropine was administered after which the sinus rhythm was transiently replaced by AV junctional rhythm with a similar ventricular rate (Fig 5*B*) Following resumption of sinus rhythm (60 to 80/minute) an advanced AV block developed together with intermittent widening of the QRS complex and ventricular premature beats (Fig 5*C* *D* and *E*) The increased duration of the QRS could be due either to an idioventricular rhythm or to aberrant conduction of the AV junctional beats Because the heart rate did not change significantly aberrant conduction is a more likely explanation for the wide QRS complex than is an idioventricular rhythm A temporary pacemaker was inserted into the right ventricle and the patient made an uneventful recovery In this case atropine improved sinoatrial conduction and sinus node automaticity and at the same time unmasked latent AV and intraventricular conduction disturbances This second effect of atropine occurred after the drug increased the sinus rate The exact localization of the block is uncertain without His bundle recording The conduction defect was probably localized below the AV node because both AV and intraventricular block were present

According to Guss and colleagues ° atropine does not significantly influence the refractoriness of right ventricular muscle This observation is consistent with the findings of Kent and co workers who showed that the parasympathetic innervation of ventricular muscle is sparse in comparison to the rich cholinergic innervation of the intraventricular conducting system

REFERENCES

1 Robinson G C and Draper G Rhythmic changes in the human heart Heart 4 9 1912
2 Wilson F N The production of atrioventricular rhythm

Annotations

Of papillary muscle dysfunction murmurs

It was not made sufficiently clear that the murmur of papillary muscle dysfunction can have almost any imaginable characteristics with regard to both the time course of intensity and/or frequency. The French clinicians were correct when they referred to the heart sounds and murmurs as noises. The only characteristics common to all papillary muscle dysfunction murmurs are that they originate from the mitral valve and are systolic in time. Thus their location and transmission and referral are the same as for any murmur of mitral insufficiency. The time course of the level of the pressure gradient across the mitral valve and the size and shape of the orifice through which the leak occurs and the time course of all three of these factors with respect to each other will determine as expected the characteristics of the murmur of papillary muscle dysfunction. This is also true of all heart murmurs.

George E. Burch, M
Tulane University School of Medic
and Charity Hospital of Lou
New Orleans

REFERENCE

1. Burch G. E., DePasquale N. P., and Phillips J. Clinical manifestations of papillary muscle dysfunc. Arch Intern Med. 112 11? 1936

Pacemaker annihilation diagnostic and therapeutic implications

Over the years clinical cardiologists have searched for electrocardiographic clues to distinguish between reentrant and pacemaker mechanisms of cardiac arrhythmias. For example it has been assumed that if a properly timed stimulus applied through external or intracardiac electrodes can terminate an episode of tachycardia then the mechanism must have been reentrant; a single stimulus would not be expected to suppress the spontaneous firing of an ectopic pacemaker. Unfortunately recent electrophysiological experiments have demonstrated that the validity of this diagnostic criterion is questionable.

Spontaneous pacemaker activity in cardiac pacemakers is characterized by rhythmic oscillations in their membrane potential. The mechanism of pacemaker depolarization in cardiac Purkinje fibers, sinoatrial nodal cells, and in working myocardial cells undergoing spontaneous activity induced by steady depolarizing current has been studied by voltage clamp experiments. In all cases pacemaker activity has been attributed to a cyclical voltage-dependent potassium current. This current has non linear features such as anomalous rectification and negative conductance and it gives the pacemaker feedback characteristics that are common to other biological oscillators. Spontaneous activity in cardiac pacemakers can be modulated by stimuli from their natural surroundings.

In general, if the spontaneous firing of a pacemaker is kicked off its stable cycle by a brief electrotonic stimulus or by a transient vagal burst it very soon resumes its previous rhythmic activity with the same cycle length but generally with a new phase in relation to the previously unperturbed rhythm. The magnitude and direction of this phase sh... depend on the time of stimulus application. This is illustr... in Fig 1A which shows a phase response curve (PPC) obt... from a spontaneously beating Purkinje fiber mounted ... sucrose gap chamber (for method, see Ref 9) and firing ... an average basic cycle length (BCL) of 1 600 msec (max... diastolic potential MDP = −8? mV). The curve shows delays and accelerations (positive and negative ΔBCL, re... tively) effected by brief depolarizing current pulses (?00 m... 0 8 μA) as functions of the time of stimulus application ... expressed as percent of BCL.

In most experiments these effects are transient and ... pacemaker rapidly returns to its free-running activity. How... er in some preparations pacemaker activity can be term... nated with a single stimulus applied at the proper time. Fig 1B shows analog records from the same experiment when the membrane potential of the pacemaker was continuo... depolarized with a bias current step of long duration. Under these circumstances MDP decreased to −?0 mV and the pacemaker was beating at an average BCL of 1 4?0 msec in the steady state. As the pacemaker cycle was scanned with a depolarizing current pulse of the same duration and magnitude as in *panel A* of Fig 1 a critical phase in the cycle was f... reached during which current pulse application was f... by subthreshold oscillations. These oscillations either beca... progressively larger and eventually reached threshold (Fig 1, *panel B2*) or they damped and resulted in complete a... tion of pacemaker activity (*panel B3* pacemaker act...

0002-8703/80/070128 + 03$00 30/0 © 1980 The C. V. Mosby C

cardiac rhythm Clin Pharmacol Ther 12 482 1971
45 Dighton D H Sinus bradycardia autonomic influences and clinical assessment Br Heart J 36 791 1974
46 Lange G Action of driving stimuli from intrinsic and extrinsic sources on in situ cardiac pacemaker tissue Circ Res 17 449 1965
47 Goldreyer B N Sinus node dysfunction A physiologic consideration of arrhythmias involving the sinus node Cardiovasc Clin 6 178 1974
48 Strauss H C Saroff A L Bigger J T and Giardina E V Premature atrial stimulation as a key to the understanding of sinoatrial conduction in man Presentation of data and critical review of the literature Circulation 47 86 1973
49 Lee C H Cohen L S and Canno D S Limitation of sinoatrial recovery time in assessing sinus node dysfunction (Abstract) Circulation 51(Suppl) II 1? 1975
50 Bashour T Hemb R and Wickramesekaran R An unusual effect of atropine on overdrive supression Circulation 48 911 1973
51 Reiffel J A Bigger J T and Giardina E G Paradoxical prolongation of sinus nodal recovery time after atropine in the sick sinus syndrome Am J Cardiol 36 98 1975
52 Scherf D The mechanism of sinoatrial block Am J Cardiol 23 769 1969
53 Dighton D H Sinoatrial block Autonomic influence and the clinical assessment Br Heart J 37 321 1975
54 Strauss H C and Bigger J T Electrophysiological properties of the rabbit sinoatrial fibers Circ Res 31 490 1972
55 Langendorf R Lester M E Plotkin P and Levin B D Atrial parasystole with interpolation Observation on prolonged sinoatrial conduction AM HEART J 63 649 1962
56 Bissett J K deSoyza N Kane J J and Smith N M Improved sinus node sensing after atropine AM HEART J 91 752 1976
57 Dhingra R C Amat y Leon F Wyndham C Denes P Wu D Pouget J M and Rosen K M Electrophysiological effects of atropine on human sinus node and atrium Am J Cardiol 38 429 1976
58 Dhingra R C Amat y Leon F Wyndham C Denes P Wu D Miller R H and Rosen K M Electrophysiological effects of atropine on sinus node and atrium in patients with sinus node dysfunction Am J Cardiol 38 848 1976
59 Narula O S and Samet P Effect of atropine and glucagon on AV nodal and His bundle pacemaker in man (Abstract) Circulation 44(Suppl II) 205 1971
60 Gupta P K Lichstein E and Chadda K Electrophysiological features of complete AV block within the His bundle Br Heart J 35 610 1973
61 Scherlag B J Lazzara R and Helfant R H Differentiation of A V junctional rhythms Circulation 48 304 1973
62 Schuilenburg R M and Durer D Conduction disturbances localized within the His bundle Circulation 45 612 1972
63 Nasrallah A T Gillette P C and Mullins C E Congenital and surgical atrioventricular block within the His bundle Am J Cardiol 36 914 1975
64 Hartzler G O and Maloney J D Intra His block with distal His pacemaker responsive to autonomic stimuli Mayo Clin Proc 52 46 1977
65 Narula O S Wenkebach type I and type II atrioventricular block (revisited) Cardiovasc Clin 6 137 1974
66 Langendorf R Cohen H and Gozo E G Observations on second degree atrioventricular block including new criteria for differentiation between type I and type II block Am J Cardiol 29 111 1972
67 Haft J I Weinstock M and DeGuia R Electrophysiologic studies in Mobitz type II second degree heart block Am J Cardiol 27 682 1971
68 Denes P Wu D Dhingra R Amat y Leon F Wyndham C and Rosen K M Dual atrioventricular nodal pathways A common electrophysiological response Br Heart J 37 1069 1975
69 Neuss H Schlepper M and Spies H F Effects of heart rate and atropine on dual AV conduction Br Heart J 37 1216 1975
70 Akhtar M, Damato A N Batsford W P Caracta A R Ruskin J N Weisfogel G M and Lau S H Induction of atrioventricular nodal reentrant tachycardia after atropine Am J Cardiol 36 286 1975
71 Denes P Wu D Dhingra R C Chuquimia R and Rosen K M Demonstration of dual AV nodal pathways in patients with paroxysmal supraventricular tachycardia Circulation 48 549 1973
72 Bailey J C, Greenspan K Elizari M V, Anderson G J and Fisch C Effect of acetylcholine on automaticity and conduction of proximal portion of the His Purkinje specialized conduction system of the dog Circ Res 30 210 1972
73 Danilo P Rosen M and Hordof A Effects of acetylcholine on ventricular automaticity Circulation 56(Suppl II) 236 1977
74 Kent K M Epstein S E Cooper T and Jacobowitz D M Cholinergic innervation of the canine and human ventricular conducting system an anatomic and electrophysiological correlation Circulation 50 948 1974
75 Waxman M B and Wald R W Termination of ventricular tachycardia by an increased vagal drive Circulation 56 385 1977
76 Gupta P K Lichstein E, and Chadda K D Chronic His bundle block Clinical electrocardiographic, electrophysiological and follow up studies in 16 patients Br Heart J 38 1343 1976
77 Danzig R Alpert H and Swan H J C The significance of atrial rate in patients with atrioventricular conduction abnormalities complicating acute myocardial infarction Am J Cardiol 24 707 1969
78 El Sherif N Scherlag B J Lazzara R Hope R, Williams D O and Samet P The pathophysiology of tachycardia dependent paroxysmal atrioventricular block after acute myocardial infarction Experimental and clinical observation Circulation 50 515 1974
79 Rosen K M Loeb H S Chuquimia R Sinno M Z Rahimtoola S H and Gunnar R M Site of heart block in acute myocardial infarction Circulation 42 925 1970
80 Guss S B Kastor J A Josephson M E and Scharf D L Human ventricular refractoriness Effects of cycle length pacing site and atropine Circulation 53 450 1976

7 Irisawa H Comparative physiology of cardiac pacemaker mechanisms Physiol Rev 58 461 1978
8 Katzung B G., and Morgenstern J A Effects of extracellular potassium on ventricular automaticity and evidence for a pacemaker current in mammalian ventricular myocardium Circ Res 40 105 1977
9 Winfree A. T Phase control of neural pacemakers Science 197 761 1977
10 Jalife J., and Moe G K Effect of electrotonic potentials on pacemaker activity of canine Purkinje fibers in relation to parasystole Circ Res 39 801 1976
11 Jalife J and Moe G K A biologic model of parasystole Am J Cardiol 43 761 1979
12 Levy M N., Martin P J Iano T and Zieske H. Paradoxical effects of vagus nerve stimulation on heart rate in dogs Circ Res 25 303 1969
13 Jalife J and Moe G K. Phasic effects of vagal stimulation on pacemaker activity of the isolated sinus node of the young cat Circ Res 45 595 1979
14 Moe G K Jalife J., Mueller W J., and Moe B A mathematical model of parasystole and its application to clinical arrhythmias Circulation 56 968 1977
15 Antzelevitch C Jalife J and Moe G K. Characteristics of reflection as a mechanism of reentrant arrhythmias and its relationship to parasystole Circulation 61 182 1980

Common sense and clinical chemistry

The evolution of clinical chemistry over the past 20 years has been a curiously uncontrolled process Clinical chemistry is an applied science whose primary function is to provide information which is relevant to the diagnosis and management of patients. Decisions about which constituents of body fluids should be measured are based on the ease with which measurements can be made and the clinical relevance of the tests Unfortunately the former consideration has always weighed more heavily than the latter As a result of the spectacular advances in methodology and automation since the 1950 s many biochemical substances can now be measured with great speed and precision The exponential growth in the workload in clinical chemistry departments which shows little sign of abating testifies to the enthusiasm with which these advances have been welcomed by both clinicians and clinical chemists Unfortunately both groups appear to have lost sight of the need for at least a modicum of clinical relevance to justify the explosion. Consequently the exponential decay rate of the proportion of tests which serve any real purpose is higher than the workload growth rate

In my own hospital in the absence of any significant changes in the management of water and electrolyte balance the numbers of plasma sodium measurements have risen by 600% over 13 years Apart from the steady rise prompted by the assumption by clinicians that they have been negligent if any patient escapes from the hospital without an electrolyte estimation there were sharp increases in 1965 when with the introduction of a new flame photometer it became automatic that the sodium was measured whenever the blood urea nitrogen was requested which doubled the sodium numbers overnight and in 197_ when a Technicon multichannel electrolyte analyzer was purchased

The workload in almost any general hospital today will be too large and the technical staff too small to make it feasible to be totally selective in biochemical tests but it is important to differentiate groups of investigations which have some functional biochemical relationship from those which are related only because of the organization of analytical machinery It is justifiable to report plasma sodium potassium chloride bicarbonate and urea nitrogen together when ever one of these tests is requested because of the way in which deviation from normality of each is often related to deviations in the others When however liver function tests are provided gratuitously whenever electrolytes are requested or the serum uric acid is automatically added to a bone profile because it is felt that all tests should be part of a profile and joints are anatomically related to bones then the clinical disadvantages rapidly outweigh the initial convenience to the laboratory and subsequently the laboratory is swamped with unnecessary repeat requests

The whole philosophy of biochemical screening is based on a failure to relate biochemical findings to the management of disease It is often suggested that one aim of clinical chemistry should be to detect and follow up disease as early as possible. Ischemic heart disease is cited as an example where a dedicated approach would be both individually beneficial and economically sound This proposal confuses theory and fact and ignores practicality There is no clearly recognized biochemical predictor of ischemic heart disease no clear line of prevention and no way of persuading patients to eat less, give up smoking worry less and exercise more even if one were convinced that these were effective measures and the implementation of such a management program would provide more than full time occupation for all the country s doctors and nurses

Even in diabetes mellitus which is the disease most likely to be revealed by biochemical screening and where there is at least a clearer although by no means absolute relationship between a single biochemical test the blood glucose and the incidence of cardiovascular renal and neurological complications there is still no evidence that the detection of an elevated blood sugar before the onset of clinical signs is of any value either in the short or in the long term

There have been several reports of the almost total failure of communication elicited by the battery of unexpected abnormal results produced with the profile screening The volume of work which this approach itself generates is considerable Of 2 000 patients who had an admission profile of 1[?] biochemical tests 3[?]% had at least one unexplained abnormal result for a test which had not been requested The immediate

0002-8703/80/070130 + 0_$00.20/0 © 1980 The C V Mosby Co

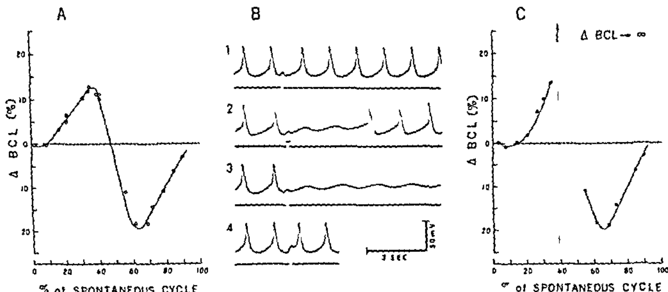


Fig 1 Phase resetting behavior of a Purkinje fiber pacemaker *A* Phase response curve (PRC) obtained from a Purkinje fiber sucrose gap preparation by scanning the pacemaker cycle with brief subthreshold depolarizing current pulses *B* Microelectrode recordings from the same preparation using current pulses of the same duration and magnitude but following a change of the steady state maximum diastolic potential to −60 mV by the application of bias current *C* PRC from a complete scan in the run illustrated in *panel B* The vertical arrow indicates the phase of the spontaneous cycle at which annihilation occurred (38%)

could be restored by the application of a second brief pulse of larger intensity) If the same stimulus (200 msec 0 8 μA) was applied at a different phase in the cycle it merely delayed (Fig. 1 *panel B1*) or accelerated (*panel B4*) subsequent discharges *Panel C* illustrates the PRC obtained under these conditions and shows that the annihilation phenomenon (ΔBCL → ∞) was only observed when the perturbing stimulus was presented between 36 and 52% of the spontaneous cycle When the duration or the amplitude of the current pulse was changed or when the membrane potential was returned to more negative levels (−64 to −91 mV) by decreasing the strength of the bias current pacemaker activity could not be terminated with a single stimulus and the PRC returned to its original shape (Fig 1A)

The phenomena we have just described are not unique to the isolated Purkinje fiber We have been able to annihilate the spontaneous rhythm of isolated SA nodal cells G Ferrier (personal communication) has obtained similar results in working muscle preparations in which repetitive activity was induced by depolarizing bias current and Wit and Cranefield have reported a similar phenomenon in simian mitral valve fibers undergoing triggered automatic activity In fact phase resetting behavior and annihilation phenomena have been observed in a variety of self-sustaining oscillatory systems including circadian rhythms neuronal pacemakers and bio chemical oscillators Common to all systems is the fact that an exact combination of stimulus timing duration and magnitude annihilates the pacemaker rhythm

Although direct extrapolation is difficult the experimental and clinical implications of these phenomena are obvious in terms of mechanism diagnosis and treatment of cardiac arrhythmias. As we have suggested in previous studies classical criteria to differentiate between reentrant and pace maker mechanisms based on the analysis of the electrocardio gram will have to be re examined The experiments outlined above further strengthen this contention and they demon strate together with the experiments of Ferrier and co workers and of Wit and Cranefield that the fact that a single stimulus can terminate a tachysystolic arrhythmia can no longer be taken as an absolute proof of reentry Further more the existence of these phenomena in cardiac pacemakers should be taken into account when analyzing the success or failure of therapeutic measures such as the drug treatment of ventricular parasystolic and other extrasystolic arrhyth mias

J Jalife MD
C Antzelevitch PhD
Masonic Medical Research Laboratory
Utica N Y 13503

REFERENCES

1 Wellens H J J Value and limitations of programmed electrical stimulation of the heart in the study and treatment of tachycardias Circulation 57 845 1978
2 Ferrier G R Saunders J H and Mendez C Cellular mechanism for the generation of ventricular arrhythmias by acetylstrophanthidin Circ Res 32 600 1973
3 Wit A L and Cranefield P F Triggered activity in cardiac muscle fibers of the simian mitral valve Circ Res 38 85 1976
4 Jalife J and Antzelevitch C Phase resetting and annihilation of pacemaker activity in cardiac tissue Science 206 695 1979
5 Noble D Cardiac action potentials and pacemaker activity *in* Recent Advances in Physiology R J Linden ed London 1974 Churchill Livingstone p 1
6 Brown H F Giles W and Noble S J Membrane currents underlying activity in frog sinus venosus, J Physiol London 271 783 1977

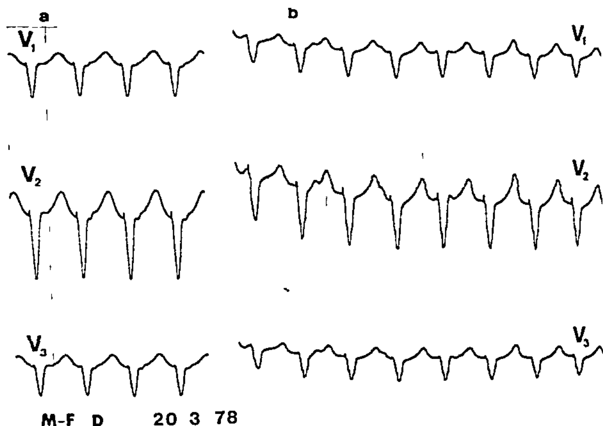


Fig 1 Patient M F D ECG recordings *a* before and *b* after lignocaine blocking of the left stellate ganglion (intracavitary stimulation at 120 impulses per minute) There is shortening of the QT interval after lignocaine

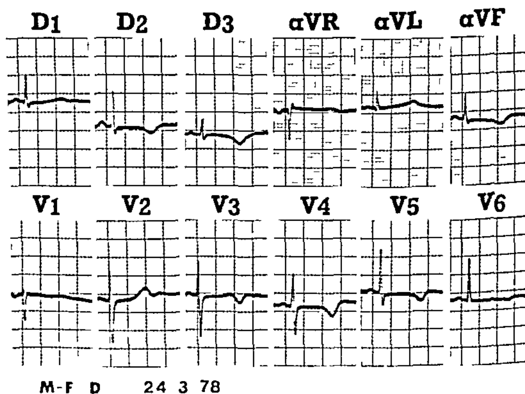


Fig 2 Same patient as in *Fig 1* ECG after left stellectomy (QT interval = 0 [illegible] sec)

implication is that every third profile will if the clinician reads the report generate the fourth However five years later follow up of 200 of this group of patients revealed that only three had results indicative of presymptomatic disease and the authors voiced doubts about the prognostic significance of early diagnosis even in these In this situation clinicians confronted with an unexpected laboratory value which deviates from the normal range rapidly learn to consider it clinically insignificant and ignore it After repeated exposure to such values they become increasingly prone to ignore everything the laboratory reports, and this includes those results which require action

On the basis that information to be transmitted to clinicians should have direct relevance to the management of their patients its quantity should be as small as possible consistent with this aim The clinical chemist s ability to generate adequate laboratory information even in relation to discretionary tests is already very considerably greater than the clinician s ability to use it The charitable urge to produce information which has not been requested because it can easily be made available should be resisted as far as possible Manufacturers of analytical machinery have stepped in with glee to profit from the loss of control of the medical profession over the investigation of their patients and have increased the momentum with which we are racing in the wrong direction by producing ever larger machines with ever more channels It is legitimate for the manufacturers to think only in terms of the money they can make Doctors should be swayed by other considerations of which not the least important is common sense

Eva Lester M B M R C Path
Consultant Chemical Pathologist
North Middlesex Hospital
London N18 England

REFERENCES

1 Barnard H F Growth of medical laboratory work during 1920–2000 Br Med J 1 383 1976
2 Lester E The machines are taking over Lancet ii 949 1979
3 Johnstone J H The organisation of clinical biochemical services in a large community (district general) hospital. *In* Recent Advances in Clinical Biochemistry editor K G M M Alberti London 1978 Churchill Livingstone p 203
4 Malins, J M Screening for disease Diabetes Lancet ii 1367 1974
5 Stowers J M Complications in relation to diabetic control *In* Complications of Diabetes editors H Keen and J Jarrett New York 1975 Edward Arnold Ltd p 3
6 Bates B and Yellin J A The yield of multiphasic screening J A M A 222 74 1972
7 Schneiderman L J De Salvo L Baylor S and Wolf P L The abnormal" screening laboratory results Arch Intern Med 129 88 19 ?
8 Whitehead T P The use of laboratory screening procedures in clinical biochemistry Biomedical Engineering 3 467 1968
9 Bradwell A R Carmalt M H B and Whitehead T P Explaining the unexpected abnormal results of biochemical profile investigations Lancet ii 1071 1974

Romano-Ward syndrome treated by left stellectomy and intracavitary stimulation

In the June 1976 issue of THIS JOURNAL we reported the case of a patient with congenital QT segment prolongation (Romano-Ward syndrome)

In view of the small number of reported cases and the uncertainties regarding the accurate treatment of that ominous disease responsible for sudden death by torsades de pointe we think it interesting to report briefly the outcome of the original mode of therapy applied in this case

The case of the patient M F D was satisfactory until January 1978 with occasional palpitations

In spite of the sustained administration of propranolol 20 mg 4 times daily and digitalin 0 1 mg five time weekly she was seized in February 1978 by short lived convulsions. In March 1978 severe and repeated spells of torsades de pointe were discovered which were abolished by a temporary intracavitary stimulation After lignocaine blocking of the left stellate ganglion a shortening of the QT interval was observed from 0 48 to 0 42 sec under intracavitary stimulation at 120 impulses per minute (Fig 1) A left stellectomy involving the inferior two thirds of the ganglion was then performed by the axillary way which resulted in an incomplete Horner s syndrome (pupillary constriction without enophtalmos or ptosis)

Subsequent ECG recordings showing a persistent lengthening of the QT interval between 0 52 and 0 60 sec (Fig 2) the installation of a permanent intracardiac pacemaker was decided upon with a programmable Cordis Omnistanicor set at 90 impulses per minute This procedure was followed by the complete disappearance of syncopes and palpitations Various ECGs and 24 hour ECG recording (Holter monitoring) revealed a good control of the rhythm by the implanted pacemaker with rare conducted atrial beats whose QT inter

Central retinal vein thrombosis in a patient with primary pulmonary hypertension

To the Editor

The etiology (primary) [illegible] in the pathogenesis of the entity.

[illegible] increased turnover [illegible] central retinal vein thrombosis [illegible] the pulmonary vasculature.

Our patient presented two years ago with [illegible] hemoptysis and [illegible] catheterization [illegible] all known reasons for [illegible] pulmonary hypertension she was [illegible] At this time [illegible] 350 mg/dl [illegible] and its turnover was [illegible] mg/ml day). The patient [illegible] years when she was presently [illegible] decrease in the vision of the left eye [illegible] vein angiography [illegible] vein.

In this patient the [illegible] significantly increased [illegible] the occurrence of venous thrombosis [illegible] patient had [illegible] the [illegible] appearance of central retinal vein [illegible] the etiology [illegible] pulmonary vasculature.

S. Bel[illegible], M.D.
[illegible], M.D.
[illegible], M.D.
[illegible], M.D.
[illegible], M.D.
Department of M[illegible]
[illegible]

REFERENCES

1. Edwards W D and Edwards J E: Clinical primary pulmonary hypertension. Circulation 56:[illegible] 1977
2. Ingelesby T V, Singer J W and [illegible] D S: Abnormal fibrinolysis in familial pulmonary hypertension. Am J Med 55 [illegible] 1973
3. Singh I and Chohan I J: Blood coagulation changes at high altitude predisposing to pulmonary hypertension. Br Heart J 34:[illegible] 1972
4. Editorial: Pulmonary [illegible] disease. Br Med J 3:[illegible] 19[illegible]
5. Deykin D: Antithrombotic therapy. [illegible] Med 65:[illegible] 1979
6. Walcott G, Burchell H [illegible] Brown A L: Primary pulmonary hypertension. Am J Med 49:[illegible] 1970

Phentolamine and IHSS

To the Editor

[illegible]

[illegible]

REFERENCES

1. M[illegible] [illegible] Am Heart J 93:[illegible] 1977
2. M[illegible] [illegible] 58 [illegible] 197[illegible]

Reply

To the Editor

We are pleased [illegible] IHSS [illegible] 1977).

These papers were not known to us at the time of publication.

[illegible]

Prophylaxis of venous thromboembolism

To the Editor

Dr. Bland [illegible] in his Editorial on [illegible] prophylaxis of deep vein thrombosis has reached some conclusions which are open to question. He suggests that a [illegible] venous thrombi are not in terms of morbidity important. If we [illegible] in a survey of the clinical features of pulmonary embolism [illegible] Bell and colleagues found that less than a quarter of their patients with angiographically proven emboli had

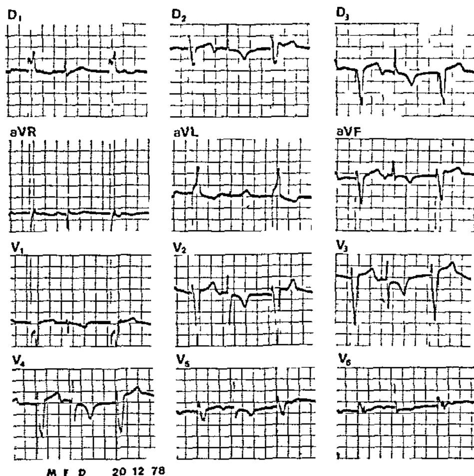


Fig 3 Same patient as in *Fig 1* The ECG shows good stimulation by the pacemaker and conducted beats with a normal QT interval

val was normal (Fig 3) To our knowledge this is the first report of left stellate ganglionectomy associated with the implantation of a pacemaker with a relatively high preset rate of stimulation This kind of treatment seems to be logical and effective Left stellectomy alone while being the treatment of choice in the Romano Ward syndrome of some authors resulted for others in inconstant improvement short lived shortening of the QT interval or even complete failure

On the other hand intracavitary stimulation prevents bradycardia common in the Romano Ward syndrome and increased by the beta blocking agents

Slow cardiac rates induce asynchronous repolarization and ectopic beats Finally thi report points to the important part played by sympathetic imbalance in the genesis of the Roma no Ward syndrome

J M Chaudron M D
E G Lebacq M.D
University of Louvain Medical Department
Hopital de Jolimont
7161 Haine Saint Paul
Louvain Belgium

REFERENCES

1 Chaudron J M Heller F., Van den Berghe H B and Lebacq E G Attacks of ventricular fibrillation and unconsciousness in a patient with prolonged QT interval A family study Am Heart J 91 783 19 6
2 Schwartz P J Periti M and Malliani A The long QT syndrome Am Heart J 89 378 1975
3 Schwartz P J Experimental reproduction of the long QT syndrome Am J Cardiol 41 374 1978
4 Yanagida H Kemi C and Suwa K The effects of stellate ganglion block on the idiopathic prolongation of the QT interval with cardiac arrhythmia (The Romano Ward syndrome) Anesthesia Analgesia 55 787 1976
5 Moss, A J and McDonald J Unilateral cervicothorac ic sympathetic ganglionectomy for the treatment of long QT interval syndrome N Engl. J Med 285 903 1971
6 Ratshin R A Hunt D Russel R O and Rackley C E QT interval prolongation paroxysmal ventricular arrhythmias and convulsive syncope Ann Intern Med 75 919 1971
7 Baudouy Ph. Andreassian B Attuel, P Greze M Soulie J and Fruchaud, J Syndrome de Romano Ward et stellectomie gauche Revue genérale à propos d un nouveau cas Arch Mal Coeur 70 645 1977
8 Schwartz P J and Malliani A Electrical alternation of the T Wave clinical and experimental evidence of its relation with the sympathetic nervous system and with the long QT syndrome Am Heart J 89 45 1975

ower limb symptoms. It appears then that asymptomatic hrombi can commonly give rise to pulmonary emboli It is ot yet possible to predict which emboli are likely to embolize Therefore for the present it is rational to consider prophylac c measures which reduce the incidence of all thrombi ymptomatic or not

Dr Blaisdell points out that the I fibrinogen uptake test ommonly used in clinical studies of thrombosis is less ensitive in the thigh and pelvic veins than it is in the calf The est is often criticized on this basis since most pulmonary mboli are said to originate in the larger more proximal veins However in an extensive autopsy series Havig found that mong 120 patients with pulmonary embolism the most roximal thrombi were below the knee in 43 cases. Twenty ve percent of lethal emboli originated in the calf Further nore it appears from venographic[4] and autopsy studies that he majority of thrombi arise in the deep veins of the calf Most thrombi involving the popliteal femoral and iliac veins re continuous with or associated with calf vein thrombi and would therefore be detected by the I fibrinogen test In view f this we conclude that for *clinical trials* of prophylactic egimes the I fibrinogen uptake test remains the method of choice for detecting deep vein thrombosis

A very useful follow up test to the I fibrinogen scan is radioisotope venography using radiolabelled macra aggregates of albumin This is less invasive than conventional x ray venography and appears to be as accurate in the thigh and pelvic veins. The radiolabelled particles cleared from the leg will also provide a perfusion lung scan It is thus a particularly valuable follow up to a positive I fibrinogen test

We agree with Dr Blaisdell that the use of standardized low doses of heparin while practical in the case of patients undergoing a routine operative procedure such as hip surgery is not reliable in patients who may be suffering from severe trauma sepsis shock, or multiple organ failure Perhaps what is needed now are trials in which the dose of heparin is adjusted for each patient to a standard end point (mean plasma heparin concentration or activity) In seriously ill patients the use of relatively noninvasive techniques such as the I fibrinogen test and the bedside isotope venogram would be essential

R J Farrell
G J Duffy MD
Department of Nuclear Medicine
St Vincent's Hospital
Dublin 4 Ireland

REFERENCES

1 Blaisdell F W Low-dose heparin prophylaxis of deep vein thrombosis An editorial AM HEART J 97 685 1979
2 Bell W R Simon, T L and de Mets D L The clinical features of submassive and massive pulmonary emboli Am J Med. 62 355 1977
3 Havig O Deep vein thrombosis and pulmonary embolism An autopsy study with multiple regression analysis of possible risk factors Acta Chir Scand Suppl 4 8 1977
4 Stamatakis J D Kakkar V V Lawrence D and Bentley P G The origin of the thrombi in the deep veins of the lower limb a venographic study Br J Surg 65 449 1978
5 Duffy G J D Auria D Brien T G., Ormond D., and Mehigan J A New radioisotope test for the detection of deep venous thrombosis in the legs Br Med J 1 712 1973
6 Bentley P G Hill P de Haas H A., Mistry F and Kakkar V V Radionuclide venography—a comparison with conventional x ray contrast venography VIIth International Congress of Thrombosis and Haemostasis Thromb Haemost 42 27 1979

Advances in the Management of Clinical Heart Disease vols II and III Edited by Jacob I Haft M D and Charles P Bailey M D Mount Kisco N Y 1978 Futura Publishing Company Vol II 308 pages Vol III 280 pages Price each volume $19 75

These two volumes represent the proceedings of the Second Saint Michael s Medical Center Cardiology Symposium on *Advances in the Management of Clinical Heart Disease* Volume II is concerned primarily with coronary heart disease viz myocardial infarction and angina pectoris The surgical and medical managements are discussed but this reviewer finds it difficult to understand the data and recommendations especially as related to the surgical results and recommendations. For example on page 298 the reference to Mullen and associates, it is stated there were no survivors in this series of 60 patients who had a low preoperative cardiac index and absent septal motion judged by the left anterior oblique ventriculogram Despite these observations their operative and late mortality was only 3 3 and 8.3% respectively Therefore what are late results? What about the interpretation of this statement? The ordinary practicing family doctor will not find this volume to be useful and the cardiologist who follows the literature already has his information and plans in practice

Volume III is concerned with three aspects of cardiovascular disease namely therapeutics hypertension and echocardiography There are rather brief discussions of the management of arrhythmias, cardiac pacing dissecting aneurysms of the aorta, valve surgery sensitivity to cardiac glycosides and hypertension and the use of echocardiography in the evaluation of valvular heart disease These presentations are intended for the practicing physician but are at the level of cardiologists to a major extent such as the use of cardiac pacing and echocardiography The family physician will learn of the recommendations and practices of the contributing authors The discussions are not presented critically for the benefit of the readers who are fully trained cardiologists These two volumes are of some interest but are not outstanding

Clinical Nuclear Cardiology Edited by Robert W Parkey M D Frederick J Bonte M D., L Maximilian Buja M D and James T Willerson M D New York 1978 Appleton Century Crofts Inc 338 pages Price $?8.50

This book describes a new subspecialty of nuclear medicine and of cardiology But is its value in clinical medicine yet established? The many contributors to this book review the field for clinicans rather thoroughly The editors of the publication fail to indicate established indications for the use of radioactive elements and nuclear medicine in cardiology The contributors do present adequately what is now the practice There is a need to know for example whether or not direct intracoronary injection of a nuclide justifies the cost and risk Furthermore it is yet to be shown that the information sought is derived or even equal to that obtained by the well established clinical procedures. Those who record electrocardiograms properly and can interpret them surely do not need myocardial imaging to detect locate and learn the size of an infarct of the myocardium Regardless the book in 15 chapters, reviews the field well. The illustrations are good and the subject is discussed so that the reader will learn applications of nuclear medicine to cardiology

Advances in Cardiology Sudden Coronary Death Vol 25 Edited by Vesa Manninen and Pentti I Halonen Basel, Switzerland 1978 S Karger AG Medical and Scientific Publishers 231 pages Price $77 00

This is another excellent volume of *Advances in Cardiology* It contains interesting and important discussions. For example physical activity and sudden death life changes and sudden death cardiomyopathy and sudden death neural influence and sudden death the role of the coronary ambulance and sudden death and the coronary care unit and sudden death are among the discussions. This is a valuable book which is easy to read and is concerned with an important problem sudden death The book should interest all doctors.

Books received

Coronary Care By Norman L. Goodland Chicago 1978 Year Book Medical Publishers Inc 88 pages

Developments in Cardiovascular Medicine Edited by C J Dickinson and J Marks Baltimore 1978 University Park Press 371 pages Price $?4.50

The New American Medicine Show By Dr Irving Oyle Santa Cruz California 1979 Unity Press 1?0 pages Price $5 95

Song of Life By Sushil K Gupta Milton Mass. 1979 Sverge Haus Publishers, 39 pages.

Computerized Tomography in Clinical Medicine By Patricia Davison Laffey M D., Wilbur W Oaks, M D R Kumar Swami M D J George Teplick M.D and Marvin E Haskin M D Philadelphia 1978 Medical Directions Inc 57 pages Price $16 00

Mechanisms of Hemostasis and Thrombosis Edited by C Harold Mielke Jr M D F A C.S and Robert Rodevien, M D Associate Editor Chicago 1978 Year Book Medical Publishers Inc 302 pages. Price $?9.95

into displacement activity keeps them too busy to deal with the business in hand—which should be preparing to go back to their lives as winners instead of losers. The physician's urging them to stay out of bed and return to work quickly colludes with their morbid desire to die rather than submit to enforced quietude. Deprived of room for maneuver[14] and having learned nothing from the experience of breaking down, they may hasten back to the same old problems with the same old tactics and break down again and again at five times the rate of their more passive (Type B) brethren who may have been overcome by chronic overloading at work, serious life dissatisfaction, bereavement, helplessness, sleeping difficulties, domestic disharmony, and attempts to adapt or habituate to life changes which outstripped their strength and coping ability.[1, 3, 21, 3] It is easy to suppose that the ability to resist a coronary breakdown diminishes as the coronary arterial abnormalities increase, but we know that it can take place irrespective of the severity of the coronary arteriographic picture[3] and many people with severe arterial abnormalities appear to lead vigorous lives and support heavy burdens without breaking down their health by forcing storms of excessive demands upon their coronary circulation.

In Schumacher's exercise we should put it down on the maps that few of the unfortunate maintain intact homeostasis before the breakdown.

Most of them have arrived at angina, acute coronary insufficiency, myocardial infarction or sudden death after a long period of exhaustion.[4] This itself causes disability because the heart rate rises excessively in response to physical and emotional challenges and the blood pressure climbs too high for too long in response to common or garden stimuli. Relatively small amounts of exercise produce the symptoms previously associated with severe effort and the coping ability is much reduced in these subjects who are played out by continuous work, disturbed sleep and continuous strain, or exhausted by constant strain day and night, affected by sleeplessness, unable to go away and leave their posts. It is now accepted that profound abnormalities of the blood lipids, sugar, uric acid, and coagulability, and defects of many other systems are likely to result from severe and prolonged struggles.[2, 1]

It is not known how exhaustion produces this condition of sympathoadrenal hyperactivity and instability,[12, 1] where homeostasis has such a weak grasp of the internal milieu, but it does seem to underlie most cases of paroxysmal arrhythmia, angina pectoris, acute coronary insufficiency and hypertension, and common sense dictates the need to reverse it before good health can be recovered. If we fail to reverse it we may be tempted to adopt symptomatic remedies such as long term beta blockade, or even open heart surgery if arteriography happens to show seductive coronary arterial narrowings.

On my map it would be shown prominently that the unfortunates who suffer a coronary breakdown in health have certain basic needs. They require adequate rest[11] and good sleep[1] to overcome exhaustion and defeat, and to recover a stronger homeostasis; it can still be taken as axiomatic that if the patient does not get sufficient sleep he will never get well.[1] They need the support of warm and close human protection during their period of helpless dependence and adequate relief of pain, anxiety and despair.[1] They need time and room for maneuver to work out where they went wrong and to choose fresh tactics for the future.[21] Usually they need a commanding influence to keep them out of the battle for long enough to get well. Above all, they need to be trained to get fit enough and tough enough to go back to their lives as winners, avoiding the old self-destructive patterns of behavior which may have been derived from a defective social education, from loneliness,[7] perhaps from growing up in a footloose society[7] or from life in an area of recent emergence from poverty.[11] Most need to improve their ability to deal with time pressures[1] and information input overloading.[21] Many have to be shown that they need not despair of becoming well merely because Aesculapians have failed to cure them with the drugs and operations which happen to be fashionable at the time.[4]

Aesculapians whose maps do not show these basic needs prominently may be ignorant of the arrhythmic hazards of emotional arousal[4] and the antiarrhythmic importance of sleep, and so they may increase the hazards of myocardial infarction by putting people into depersonalised intensive care units amongst frightening technological paraphernalia. They may compare the effects of one

American Heart Journal

August 1980 Volume 100 Number 2

Editorial

The responsibility of the cardiological mapmaker

P G F Nixon F R C P
London England

> The task of the philosopher is to provide a map of life and knowledge which exhibits the most important features of life in their proper prominence
>
> E F Schumacher 1977[1]

E F Schumacher suggests that the last three centuries of aggressive scientific imperialism have given us bewildering maps which omit most of the features that really matter because the mapmakers have concentrated on things which allegedly could be proven their first principle was If in doubt leave it out Since the question of what constitutes proof is subtle and difficult Schumacher recommends the exercise of turning the principle into its opposite and saying If in doubt show it prominently This exercise is useful to the cardiologist because his clinical duties oblige him to deal with large and important features which cannot yet be measured (unless he restricts his life to the laboratory) and as a mapmaker for patients and students he cannot evade his obligations to point out the routes of choice

In the coronary field the first step in the exercise must be for the cardiologist to decide whether he is an Aesculapian godsent to cure the disease or a disciple of Hygeia believing that his main responsibility is to find out where the patient s life went wrong and teach him how to get back on the good health which was his birthright After half a century of neglect it looks as though Hygeia may come into her own again because doctors who can enter into their patients lives are still insisting that behavior and circumstances can have profound effects upon the cardiovascular system and science is providing increasing support for their opinions by revealing the morbid effects of some aspects of life experience in susceptible persons

In this exercise our maps should show quite plainly that many coronary patients have a behavior problem and the younger they suffer the coronary breakdown the more serious the problem is likely to be Most of them are strivers and achievers restlessly addicted to work and tension guilty when wasting a minute enjoying the attack but never gratified by achievement (Type A) and capable of driving themselves far beyond the range of their homeostasis s ability to maintain a normal internal milieu[6 7 13 1 3 6 33] The coronary breakdown is often their comeuppance occurring either when they allow themselves to suffer defeat at the hands of others or when they defeat themselves by running out of time or strength[1 3] There are a number of good reasons why they consistently conceal this from the interrogator the burdens of explanation are too great[31] denial moves in to conceal their inadequacies from themselves and others[11 31 3 3] arrhythmic and self destructive life styles are presented as normal and the psychological need for escape

From the Cardiac D partm nt Charing Cross Hosp tal (Fulham) Lo d n England

Received for publicat on Jun 29 1979

R print requests Dr P G F Nix n Consultant Cardiologist Charing Cross Hosp tal (Fulham) Fulham P l ce Rd Hamm rsmith, Lond n W6 8RF Engl nd.

000? 8 03/80/080139 + 05$00.50/0 © 1980 The C V Mosby Co

Schumacher s exercise of showing prominently the features which many omit from their maps because they regard them as in doubt unmeasured and unproved The emotional reaction of the reader is more likely to depend upon his philosophy than upon the measured and proved needs of his patients Is this as it should be?

REFERENCES

1 Schumacher F F A Guide for the Perplexed London 1977 Jonathan Cape
2 Latham P M Diseases of the Heart London 1845 Longman Brown Green & Longmans
3 Steell G Text Book on Diseases of the Heart Manchester 1906 Manchester University Press
4 Mackenzie J Diseases of the Heart London 1908 Hodder & Stoughton
5 Brunton T L Collected Papers on Circulation and Respiration London 1916 MacMillan and Company Ltd
6 Dunbar F Psychosomatic Diagnosis New York 1943 Paul B Hoeber Inc Reprinted New York 1968 Johnson Reprint Corporation
7 Arlow J A Identification mechanisms in coronary occlusion Psychosom Med 7 195 1945
8 Wood P Diseases of the Heart and Circulation London 1956 Eyre & Spottiswoode
9 Raab W Preventive Cardiology Springfield Illinois 1966 Charles C Thomas Publisher
10 Russek H I Role of emotional stress in the etiology of clinical coronary heart disease Dis Chest 52 1 1967
11 MacKinnon A U The psychopathology of ischaemic heart disease J R Coll Practit 16 2 3 1968
12 Wolf S Psychosocial forces in myocardial infarction and sudden death Circulation 39(Suppl 4) 74 1969
13 Carruthers M F Aggression and atheroma Lancet 2 1170 1969
14 Bellet S Roman L and Kastis J The effect of automobile driving on catecholamine and adrenocortical excretion Am J Cardiol 24 365 1969
15 Levi L (Editor) Society Stress and Disease London 1971 Oxford University Press
16 Levi L (Editor) Stress and Distress in Response to Psychosocial Stimuli Oxford 1972 Pergamon Press Inc
17 Burch G L and Giles T Aspects of the influence of psychic stress on angina pectoris Am J Cardiol 31 108 1973
18 Friedman M and Rosenman R H Type A Behaviour and Your Heart London 1974 Wildwood House
19 Kagan A R and Levi L Health and environment—psychosocial stimuli a review Soc Sci Med 8 225 1974
20 Clark D A Arnold F L Foulds F I Brown D M Eastmead D R and Parry F M Serum urate and cholesterol levels in Air Force cadets Aviat Space Environ Med 46 1044 1975
21 Lipowski Z J Sensory and information inputs overload behavioural effects Compr Psychiatry 16 199 1975
22 Eastwood M R The Relation Between Physical and Mental Illness Toronto 1975 University of Toronto Press
23 Gentry W D and Williams R B Psychological Aspects of Myocardial Infarction and Coronary Care Saint Louis 1975 The C V Mosby Company
24 Theorell T and Rahe R H Life change events ballistocardiography and coronary death J Human Stress 1 18 19 5
25 Theorell T Selected illnesses and somatic factors in relation to two psychosocial stress indices—a prospective study on middle aged construction building workers J Psychosom Res 20 7 1976
26 Nixon P G F Human function curve with special reference to cardiovascular disorders Practitioner 217 765 935 1976
27 Croen J J Psychosomatic aspects of ischaemic (coronary) heart disease in O Hill ed., Modern Trends in Psychosomatic Medicine London 1976 Butterworth Co Ltd
28 Lynch J The Broken Heart New York 1977 Basic Books Inc
29 Henry J P and Stephens P M Stress, Health and the Social Environment New York 1977 Springer Verlag
30 Chis D C Behaviour Patterns Stress, and Coronary Disease New York 1977 John Wiley & Sons Inc
31 Finlayson A and McEwen J Coronary Heart Disease and Patterns of Living London 1977 Croom Helm Ltd
32 Rahe R H and Ransom R J Life change and illness studies past history and future directions J Human Stress 4 3 1978
33 Jenkin C D Behavioural risk factors in coronary artery disease Ann Rev Med 29 543 1978
34 Hackett T P and Cassem N H Factors contributing to delay in responding to the signs and symptoms of acute myocardial infarction Am J Cardiol 24 651 1969
35 Croog S H Shapiro D S and Levine S Denial among male heart patients Psychosom Med 33 385 1971
36 Corlin R Coronary Artery Disease Philadelphia 197 W B Saunders Company
37 Crooner M F Jernigan J A and Martin C E Variations in serum lipid concentration and clinical coronary disease Am J Med Sci 239 133 1960
38 Nixon P G F and Bethell H J N Preinfarction ill health Am J Cardiol 33 446 1974
39 Feinleib M, Simon A B Gillum R F and Margolis R Prodromal symptoms and signs of sudden death Circulation 51 and 52(Suppl 3) 153 1975
40 Lewis T The Soldiers Heart and the Effort Syndrome London 1918 Shaw & Son Ltd
41 Fancheri F Bellaterra M Matteoli S Cristofani Polizzi C, and Puletti M Infarct as a stress agent life history and personality characteristics in improved versus non improved patients after severe heart attack J Human Stress 4 16 19 8
42 Burch C F Of pre infarct syndrome and bed rest Am Heart J 94 2 1977
43 Gibson C A The Nervous Affections of the Heart Edinburgh 1904 Young J Pentland
44 Nixon P G F Treatment of Arrhythmia and Pacing in Bouchier I A D ed Seventh Symposium on Advanced Medicine London 1971 Pitman Medical
45 Taylor Lord Poverty wealth and health or getting the dosage right Br Med J 2 707 19 5
46 Edwards R Coronary Case London 1964 Faber and Faber Ltd
47 Lown B De Silva R and Lenson R Roles of psychologic stress and autonomic nervous system changes in provocation of ventricular premature complexes Am J Cardiol 41 979 1978
48 Harrison D C Fitzgerald S W and Winkle R A Contribution of ambulatory electrocardiographic mon

antiarrhythmic drug with another and never state whether their acute care units help the recovery of homeostasis or incubate sudden death After the acute phase of the illness they may provide a relatively inflexible program of activity[5] which scarcely fits any particular patient because they think of themselves as dealing with a disease and not as serving people with infinitely variable coping abilities and circumstances

These Aesculapians can make extraordinary errors with patients suffering from angina pectoris because their maps do not show that the majority will get well if they follow the ancient rules of taking care to sleep well to avoid exhaustion and above all to avoid producing angina[2, 4, 8, 3, 31, 5] each attack of which overdistends the left ventricle and creates the risk of replacement fibrosis or fatal arrhythmia [31] Instead of being given the ancient rules the patient is likely to be given a map which overemphasizes risk factors of dubious value[33] Far from attending to the basic needs and encouraging obedience to the ancient rules the Aesculapian may create drug trials in which the patient is actually *encouraged* to produce pain in his daily life and invited to keep a trinitrin count[1] And once again the published trials compare one drug with another but not with the effect of taking care of the basic needs and following the ancient rules

If the angina worsens because the patient is not taught how to get well the Aesculapian assumes that the disease has got worse escalates the investigations and therapy and begins to discuss the implications of surgical treatment This approach may increase the anxiety and the relative coronary insufficiency and precipitate a breakdown—a tragedy if all the patient really needs is the removal of exhaustion and hyperarousal and the provision of good sleep to enable the demands upon the heart to fall back within the area of coronary competence[5]

An important feature of the cardiologist s map has always been iatrogenic disorder and in my opinion this has been expanded beyond belief by the beta blockers It is now commonplace to encounter the expected and reversible complications of reduced cardiac output such as cerebral vascular insufficiency intermittent claudication weakness tiredness and inability to cope with tasks and a frequent cause of consultation is the patient s inability to convince his doctor that the beta blocker is doing nothing to halt his deterioration towards a second or third myocardial infarction In some cases the doctor thought the drug effects were caused by arteriosclerotic deterioration In other cases he has recognized the noxious effects of his therapy but the propaganda has made him fear to stop it All too often the doctor was so persuaded of his drug s virtues that he closed his mind to his patients heretical reports[34]

It is time someone put on the map the belief that it might not be dangerous to stop beta blockade provided that sleep deprivation exhaustion and morbid arousal have been dealt with first[5] I regard it as essential to stop beta blockers during my preparation of a cardiac patient for training at the gymnasium Beta blockers may increase effort capacity by 25 to 50% in angina pectoris[35] which is negligible by our standards but they fail to prevent the left ventricular end diastolic pressure from rising too high with exercise[36] It is this excessive rise of pressure which increases the left ventricular wall tension creates patchy ischemia and invites arrhythmia and sudden death and which also stiffens the pulmonary venous system thereby creating unpleasant dyspnea instead of pain in some cases Furthermore beta blockade restricts the freedom of the heart rate to rise and so removes our simplest guide to the net effect of exercise fatigue and emotional arousal during cardiac rehabilitation

Coronary artery bypass grafting must have a place on the cardiologist s map because it exists so widely and profitably and because it has such a large industry growing up about it It is a pity that the evaluation has been so poor[6] because its logic is unappealing Some people generate angina get over their troubles and recover Others keep it going for years aggravate it at will and crash into infarction and sudden death almost regardless of the appearances of the coronary arteries and myocardium when they begin their careers of ill health pain and disability[3] The operation may bypass some of the debris and damage accumulated during their arteriopathic catecholamine storms but how can it teach them to survive? It is surprising how uncommonly surgical treatment is sought when a strong and humane attempt has been made to meet the basic needs and to teach the ancient rules of angina

This editorial is one cardiologist s attempt at

Early diagnosis of pericarditis in acute myocardial infarction

Jaber I Sawaya M D
Salim K Mujais M D
Haroutune K Armenian M D Dr P H
Beirut Lebanon

Although pericarditis developing during the acute phase of myocardial infarction has not been shown to substantially increase the hospital mortality rate[1-6] recognition of this complication remains important in order to avoid other diagnostic possibilities including extension of the infarction and extensive myocardial damage based on the elevation of the ST segment[7]

The purpose of this study is to explore the predictive value of several factors in the patient s profile that can alert the physician to the early diagnosis of pericarditis in acute myocardial infarction The value of salicylate treatment is also assessed in these patients with a review of the literature

Materials and methods

Data on all patients admitted to the Coronary Care Unit of the American University Hospital between July 1 1977 and December 31 1978 were stored on a system 3 digital computer Two hundred and sixty one patients had unequivocal evidence of acute myocardial infarction based on at least two of the following criteria (1) typical history of prolonged coronary pain (2) evolution of ST T wave changes and abnormal Q waves and (3) significant rise in serum enzymes creatinine phosphokinase (CPK) as determined by the method of Okinaka and associates glutamic oxaloacetic transaminase (GOT) and lactic dehydrogenase (LDH) frequently with isoenz determinations Patients were continuously m itored between 3 and 5 days and on subseq days when major complications developed 12 lead electrocardiogram was recorded daily 3 days on all patients and daily thereafte pericarditis or other major complications curred A portable chest x ray was done admission and was repeated at least once du the hospital stay Serum enzymes were de mined on admission and for 3 consecutive d Subsequent determinations were done if ex sion of infarction was suspected or when peri ditis developed The patient s demographic clinical characteristics coded and stored in computer included the following age sex qu of pain on admission previous history of coro pain location of the infarction previous d mented myocardial infarction and delay admission to the hospital in hours Complicat previously established to occur in acute myo dial infarction were also identified Indivi arrhythmias are classified according to Ch and ventricular arrhythmias were graded acc ing to a modification of Lown and associat Primary ventricular fibrillation was diagn when the arrhythmia occured within 48 h from admission and secondary ventricular fi lation was diagnosed when this arrhyth occurred in the setting of pump failure afte hours Fascicular blocks were diagnosed acc ing to the criteria of Rosenbaum and colleag Heart failure was classified according to criteria of Killip and Kimball[13] Blood lipid ab malities were classified according to Frede son Other stored information included intake established coronary heart disease

From the Division of Cardiology Department of Internal Medicine and the Department of Epidemiology and Biostatistics, American University of Beirut Hospital, Beirut, Lebanon

Received for publication Sept. 13 1979
Accepted for publication March 3 1980

Reprint requests Jaber I Sawaya M D Division of Cardiology American University Hospital, Beirut, Lebanon.

0002-8703/80/080144 + 08$00 80/0 © 1980 The C. V. Mosb

toring to antiarrhythmic management Am J Cardiol 41 996 1978
49 *Report of First W H O Interdisciplinary Workshop on* Psychosocial Factors and Health Stockholm 1976 WHO Geneva
50 Scherf D and Cohen J To each according to his desert AM HEART J 95 536, 1978
51 Broadbent W H and Broadbent J F H Heart Disease with Special Reference to Prognosis and Treatment London 1897 Bailliere Tindall & Cox
52 Lewis T Disease of the Heart London 1933, Macmillan & Co Ltd
53 Corday E and Corday S R Prevention of heart disease by control of risk factors the time has come to *face the facts*. *Am J Cardiol* 35 330 1975
54 Nixon P G F Clinical cardiology and The Lancet Lancet 1 438 1979
55 Turner G C., Nelson R R., Nordstrom L. A., Diefenthal, H C and Lobel, F L. Comparative effects of nadolol and propranolol on exercise tolerance in patients with angina pectoris Br Heart J 40 1361 1978
56 Preston T A Coronary Artery Surgery A Critical Review New York 1977 Raven Press

IMPORTANT
INFORMATION FOR AUTHORS

Effective June 1 1980 all manuscripts for the AMERICAN HEART JOURNAL should be sent to

Dean T Mason M D
Section of Cardiovascular Medicine
University of California
School of Medicine
Davis California 95616

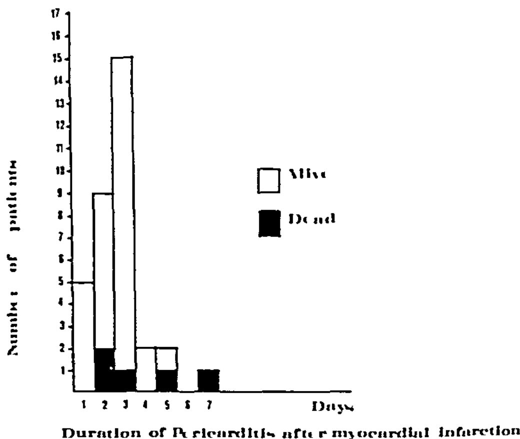


Fig 2 Duration of pericarditis after myocardial infarction

$$Y = a + b_1X_1 + b_2X_2 + \dots b_nX_n$$

Where Y is the dichotomous dependent variable indicating the presence or absence of pericarditis the b s are the regression coefficients, The X s are the independent variables, and *a* is the constant

Using such a technique it was possible to calculate for each of the variables the proportion of the variation explained by the factor under consideration

Results

Clinical characteristics and risk factors Of the 261 patients with acute myocardial infarction 38 with transmural myocardial infarction had pericarditis (14.5%) All patients were males. Some of the clinical features are shown in Table I A comparison between the pericarditis patients and their controls did not reveal any significant difference as to the character of chest pain on admission, history of previous myocardial infarction or angina, or the location of infarction A confirmatory two-component friction rub was audible in all patients this occurred between the second and fourth day from the onset of myocardial infarction pain in 33 patients In none of the patients did friction rub appear after the fifth day (Fig 1) In the majority of the patients who died the pericarditis lasted longer than 3 days (Fig 2)

Considering that the pericarditis in the patients was caused by the pathological processes related to the myocardial infarction the latent period between the onset of symptoms of myocardial infarction and the onset of pericarditis was calculated as an expression of the incubation period of pericarditis Using the method of Sartwell as applied to non infectious diseases,[a] the median incubation period and its dispersion factor were calculated for pericarditis following myocardial infarction based on our own data and on data from Lichstein and co workers[3] The estimated median incubation period was 42 hours with a dispersion factor of 1 53 Thus about 95% of the pericarditis is expected to develop between 1 and 95 hours from the onset of the myocardial infarction

Twenty nine pericarditis patients had congestive heart failure Killip s class II or above compared to 15 matched controls. This difference was statistically significant (Table II) Radiological

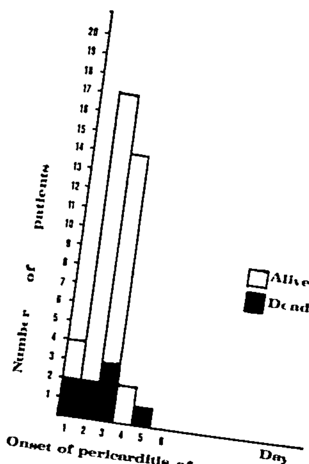


Fig 1 Onset of pericarditis after myocardial infarction

factors hospital stay in days and mortality status A detailed problem oriented medical record was constructed on each patient which permitted accurate and frequent documentation of events No postmortem studies were done

The diagnosis of pericarditis (AMI P) was made when a two component friction rub was heard by the house staff and was confirmed by at least one senior cardiologist Those who developed a friction rub after cardiopulmonary resuscitation were not included in the study Patients with pericarditis and controls were examined several times a day

Each case of pericarditis (AM P) was matched with one control of the same age and sex from the remaining 223 patients with acute myocardial infarction but with no evidence of pericarditis Thus 38 controls (AMI C_1) were selected at random either from the dates preceding or following the date of admission of the case of pericarditis

As an initial step in analyzing the data comparisons were made between the cases of pericarditis and the remaining group of acute myocardial infarction patients with no pericarditis (AMI C) in addition to the case control comparisons between AMI P and AMI C The percentage distributions of cases and controls were calculated for each characteristic and a matched pair analysis was done for the comparison of AMI P and AMI C Such comparisons were used to assess variables that could have a predictive value in identifying patients admitted to the coronary care unit who are at risk of developing pericarditis as a complication of acute myocardial infarction

In addition using the Statistical Package for the Social Sciences Program a stepwise multiple regression analysis was done In order to develop a predictive model for pericarditis in acute myocardial infarction the effect of significant independent variables was assessed in a stepwise manner adding one variable at a time Thus the predictive value of each of these variables could be assessed following adjustment for the rest of variables The model used was

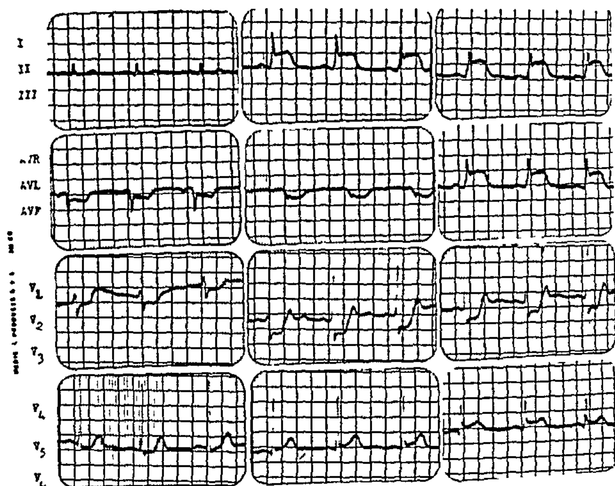


Fig 3 Twelve lead electrocardiogram showing acute inferior myocardial infarction with reciprocal change

Table III Percent frequency of complications in pericarditis and controls

	AMI P	AMI C_1	AMI C_2
Cardiomegaly	21	18	17
S gallop	21	10	7
Papillary muscle dysfunction	15	5	7
Cardiac arrest	13	3	11
Pneumonia	13	10	7
Extension of infarction	5	5	3
None	0	34	33

Table IV Peak serum enzyme levels in patients with pericarditis and their matched controls

Enzyme	AMI P (mean ± SD)	AMI C_1 (Mean ± SD)	t	P
CPK	50 4 ± 27 1	37 6 ± 23 3	2 20	< 0 05
LDH	1 863 9 ± 847 7	1 343 5 ± 732 7	2 66	< 0 05
SGOT	123 7 ± 69 4	94 6 ± 103 8	1 62	N S

Mortality Eight (21%) of the pericarditis g died in the hospital compared to 5% in matched control AMI C_1 ($P < 0.01$) The h tal mortality rate of all the myocardial infar patients without pericarditis was 17% and difference was not significant compared to pericarditis patients (Table VI)

Discussion

Pericarditis in myocardial infarction has clinically recognized to occur between 6 8% 16% in various series[1,5,7] while in an aut series 80% of patients with myocardial infar had pericardial involvement [1] This discrep might be attributed to (1) inadequate docume tion in clinical retrospective studies (2) the f ing nature of the diagnostic pericardial fric rub and (3) the lack of predictive factors alert the coronary care staff to the patient at risk of developing pericarditis

The higher incidence of pericarditis in our compared to other clinical studies (Table

evidence of congestive heart failure included pulmonary congestion (10 patients), acute lung edema (three patients), and cardiomegaly (two patients). *In addition, six pericarditis patients* had a combination of infiltrates, atelectasis, or pleural effusion. Seventeen patients had normal chest x-rays.

In six patients diffuse ST segment elevation typical of pericardial inflammation was noted at the time pericarditis was diagnosed clinically (Figs. 3 and 4). In the rest of the patients the appearance of the rub was not associated with any significant ST shifts. In patients with anterior infarction the peak ST elevation measured within 24 hours from onset was 5.9 mm for AMI-P compared to 2.8 mm in AMI-C_1 ($P < 0.01$). For patients with inferior infarction these averages were 2.9 and 2.2 mm, respectively ($P < 0.05$).

All patients with pericarditis had one or more complications of myocardial infarction, while at least one third of the controls were free of complications (Table III). Twenty-four pericarditis patients had sinus tachycardia compared to 13 of the matched controls. There was no difference in the occurrence of supraventricular or ventricular arrhythmia, atrio-ventricular or fascicular blocks. The two groups did not differ significantly as to the presence of the following risk factors: diabetes, hyperlipidemia, hypertension, smoking, positive family history of coronary heart disease, hyperuricemia, and obesity.

Laboratory results. Pericarditis patients had significantly higher mean values of peak CPK and LDH compared to the matched controls ($P < 0.05$), as shown in Table IV. SGOT peak values did not show such a difference. Six out of eight pericarditis patients who died had CPK values higher than 60, while only five of the 30 surviving had such high values of CPK ($P < 0.01$).

Multiple regression analysis. *In an effort to* assess the predictive value of these clinical and laboratory findings for pericarditis in acute myocardial infarction, a stepwise multiple regression analysis was done using the presence or absence of pericarditis as the dependent variable and the Killip's classification for congestive heart failure, the peak ST segment elevation in millimeters within 24 hours from onset, and the peak values for LDH, CPK, and SGOT as the independent variables. As illustrated in Table V, following multiple adjustment, the variable that could explain more of the variation as to the development of pericarditis was the ST segment elevation, and a significant contribution by this variable was maintained throughout the stepwise multiple regression analysis. The regression coefficients for the peak enzyme values and the Killip's classification for congestive heart failure were small and not significant and were of minimal predictive value.

Treatment. Thirty-one patients were treated with salicylates at an average dose of 2 to 3 grams per day for 10 to 14 days. Response was satisfactory in 27 patients (87%) with prompt and sustained relief of pain without complications. Follow-up at 3 weeks following discharge did not show recurrence of pericarditis or the development of postmyocardial infarction syndrome.

Table I. Clinical characteristics of patients with pericarditis (AMI-P) and matched controls (AMI-C_1)

	AMI-P (No.)	*AMI-C_1 (No.)*	*Total MI (No.)*
Total patients	38	38	261
Previous MI	8	7	52
History of angina	22	23	155
Typical pain on admission	36	31	217
Location of MI			
Anterior	24	21	118
Inferior	12	12	97
Mixed	2	1	46
Hospital mortality	8	2	46
Admission to hospital within 6 hr	24	22	155
Mean age ± SD (days)	58 ± 10.33	58 ± 10.28	57.6 ± 11.95
Mean length of stay ± SD (days)	1[illegible]4 ± 5.5	11.6 ± 7.9	10.3 ± 6.0

Table II. Killip's classification of heart failure in AMI-P and AMI-C_1

	Killip's Class				
	I	*II*	*III*	*IV*	*Total*
Pericarditis	9	22	6	1	38
Controls	23	9	5	1	38

$\chi^2 = 11.66$, $df = 3$, $P < 0.01$

Table VI Percent mortality in pericarditis and controls after M I in various series

Series	Total number of pericarditis patients	Death in pericarditis		Death in controls (%)
		No	%	
Thadani et al	52	10	19	13
Toole et al	40	8	20	12
Niarchos et al	22	4	18	12
Barman et al	106	18	17	10
Lichstein et al	31	5	16	12
Liem et al	44	2	5	7
Guillevin et al	64	—	2	26
Present series	38	8	21	5 17†

Mortality in age and sex matched control

†Mortality in all patients with acute MI without pericarditis.

Table VII Clinical incidence of pericarditis complicating MI*

Series	Total MI	Pericarditis	Incidence (%)
Thadani et al	709	52	6 8
Toole et al	551	40	7.2
Niarchos et al	195	22	11 3
Barman et al	1 284	106	8 3
Lichstein et al	305	31	10 1
Liem et al	300	44	14 7
Guillevin et al	400	64	16 0
Present series	261	38	14.5
Cumulative	4 078	397	11 1

MI myocardial infarction

mapping studies and the standard six lead precordial electrocardiogram improves the value of the latter tool in the diagnosis of pericarditis

Sinus node and atrial irritation described by James in patients with pericarditis increase the vulnerability to supraventricular arrhythmia Arrhythmias are rather common complications in myocardial infarction Most studies unlike ours have indicated a high incidence of arrhythmia in patients with pericarditis

Our findings of increased pump dysfunction in patients with pericarditis are in agreement with previous observations This dysfunction is a reflection of increased myocardial damage in these patients manifested by the pericardial involvement The appearance of the pericardial rub within a few hours from the onset of myocardial infarction probably carries a grave prognosis

It is important to note that in the multiple linear regression analysis the variable that could explain more of the variation as to the development of pericarditis was the ST segment elevation The finding that the extent of CPK LDH and SGOT elevation and degree of pump dysfunction did not contribute significantly to explain the variation in this model may be due to the fact that ST segment elevation has measured the same myocardial changes that are expressed by enzyme elevations and pump dysfunction Thus, ST segment elevation in itself is possibly a better clinical indicator of these changes under these circumstances Only 35% of the variation could be explained between pericarditis patients and their controls using the above mentioned variables Further studies need to be done to investigate the possible role of other variables and indicators in this condition

Summary

Pericarditis complicating acute myocardial infarction assumes increasing importance in this era of quantitating infarct size by precordial ST segment mapping Early recognition of this complication avoids diagnostic and therapeutic errors In this study we looked for factors that could alert to the early diagnosis of pericarditis such as ST elevation measured within 24 hours from onset extent of CPK LDH and SGOT elevation as well as degree of pump dysfunction ST segment elevation in millimeters on admission seemed to be one factor that was of predictive value in this condition

Pericarditis occurred in three forms (1) within a few hours from the onset of myocardial infarction and this form seems to carry a high mortality rate (2) a more common variety occurs within 24 to 72 hours from onset and carries a higher mortality rate than matched controls and (3) the late syndrome of Dressler s not observed in our series Aside from increased incidence of heart failure other complications of myocardial infarction and the coronary risk factors were not significantly higher in patients with pericarditis Salicylate treatment offers immediate relief in the majority of patients

REFERENCES

1 Thadani U Chopra M P Aber C P and Portal R W Pericarditis after acute myocardial infarction Br Med J 2 135 1971

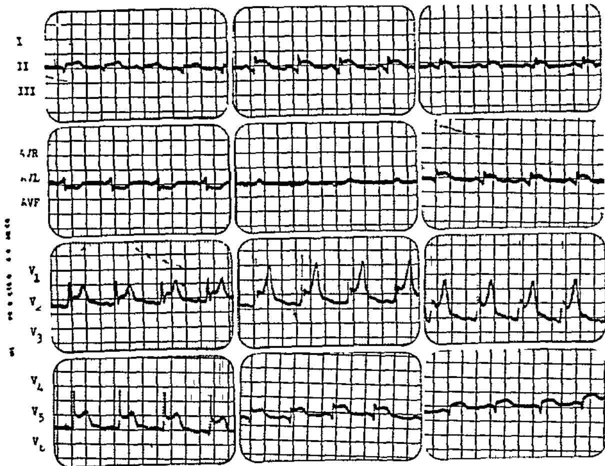


Fig 4 Electrocardiogram (in the same patient as in *Fig 3*) 72 hours later showing diffuse ST T wave changes of pericarditis

may in part reflect the prospective nature of the study similar to the findings of Liem and colleagues and Guillevin and Valere [3] This increased yield may also be due to the heavy staffing of our Coronary Care Unit As in other studies the friction rub appeared between the second and fourth day in the majority of patients In two patients the friction rub appeared within 4 hours from the onset of myocardial infarction and both of these patients died The early appearance of the rub in these patients probably reflects more extensive myocardial damage Five out of six patients whose rub persisted beyond 3 days died This tendency was also noted in other studies [1] There was no recurrence of the rub or appearance of Dressler's syndrome at 3 weeks following discharge an encounter noted by Niarchos and McKendrick but at variance with earlier reports [1] The findings of high CPK and LDH values in the pericarditis patients are in agreement with those of Thadani and colleagues The extent of myocardial cell damage has been

Table V Results of multiple linear regression analysis

Variable	*b*	*S E b*	*P*	*Percent of variation explained*
ST elevation	0.1062	0.0273	< 0.001	3[illegible]0
Peak LDH	0.0001	0.0001	N.S	1.4
Killip's Class	0.0[illegible]06	0.0665	N S	1.0
Peak SGOT	0.0006	0.0006	N S	0.9
Peak CPK	0.0009	0.00[illegible]8	N.S	0.1
Constant	0.0739			

correlated with the magnitude of ST segment elevation [25] Lichestein[5] reported more marked ST segment shifts in their patients with pericarditis Hardarson and co workers [6] and Zmyslinski and colleagues noted a secondary rise of persistent ST elevation in the patients who developed pericarditis studied by precordial mapping The good correlation demonstrated between precordial ST

Evaluation of the anatomy of congenitally malformed aortic valves by orifice view aortography

Gordon M Folger Jr MD *
Hani N Sabbah BS
Paul D Stein MD
Detroit Mich

Employing a cineaortographic technique whereby the patient is rotated so as to cause en face viewing of the aortic valve[1,2] it is possible to determine aortic valve area accurately This technique of orifice view aortography is particularly useful in children where the assessment of aortic stenosis often necessary prior to the development of symptoms is at times difficult and occasionally not possible by conventional means[3] Of considerable importance in such individuals may be knowledge of aortic valve anatomy especially as it pertains to operability by simple valvular commissurotomy as opposed to aortic valve replacement

This study presents the results of a critical review of our experience using this technique with congenital aortic valvular malformations in regards to the ability to delineate accurately the appearance of the aortic valve

Materials and methods

Nineteen patients with clinical findings indicative of congenital aortic valve malformations were studied The age of the patients ranged from 11 to 36 years average 19 years The technique and method of photographing the aortic valve en face has been previously described in detail[1] and the technique for positioning the U arm angiographic system to achieve this view has also been described Briefly the patient is positioned on the angiographic table in the direct right lateral projection and the table is angulated 35 to 40 degrees off the vertical causing the x ray beam to travel essentially from the right axilla to the left iliac crest Aortography is then performed with a standard catheterization technique the tip of the catheter being positioned in either sinus of Valsalva The aortic valve is thus viewed as though looking into the aorta as it exits the heart The orientation of the valve on the film is such that the right and left aspects are respectively to the viewer s right and left the superior and inferior aspects respectively represent the anatomic anterior and posterior aspects[1]

The congenitally abnormal aortic valves were all viewed in this manner and were analyzed for configuration including the number of commissures and thus the number of functioning leaflets the appearance and position of each leaflet the presence or absence of an identifiable leaflet raphe the appearance and position of the valve orifice and the number as well as sinus of origin of the coronary arteries Each was also analyzed for the presence of aortic regurgitation without consideration to degree In addition the area of each valve leaflet was planimetered and expressed as a ratio of the larger to the smaller leaflet regardless of their relative positions

Thirteen patients had clinical and hemodynamic evidence of congenital valvular aortic stenosis with or without associated regurgitation as their only identifiable abnormality The remaining six patients had other associated malformations of the heart including four individuals with coarctation of the aorta and one each with fixed

From the D partm nt f 1 1 t Me h in nd Surg ry Henry Ford Ho pital Detroit Mich

Supported by Pr j t R388 0 f m funds supplied by Henry Ford Ho pital through a g nt fr m th Ford F u dat n New York N Y

Received f r publicati n N 13 1 9

Accepted for publication J 3 1980

Reprint requests Gordon M Folger Jr MD Dept f 1 1 tri Henry Ford Ho pital 2799 W Grand Bl d Detroit Mich 48 0

*Director Clinic for Children with Cardiovascular Diseases Department of Pediatrics Henry Ford Hospital

0002 8703/80/080152 + 09$00 80/0 © 1980 The C V Mosby Co

2 Toole J C and Silverman M E Pericarditis of acute myocardial infarction Chest 67 547 1975
3 Niarchos, A P and McKendrick C S Prognosis of pericarditis after acute myocardial infarction Br Heart J 35 49 1973
4 Barman P C Krishnaswami, V and Geraci A R Pericarditis in acute myocardial infarction N Y State J Med 72 645 1973
5 Lichstein E Liu Ho mau and Gupta P Pericarditis complicating acute myocardial infarction Incidence of complications and significance of electrocardiogram on admission AM HEART J 87 246 1974
6 Likoff W Pericarditis complicating myocardial infarction Am J Cardiol 7 69 1961
7 Reid P R Taylor D R Kelly D T Weisfeldt M L Humphries, J O Ross R S and Pitt B Myocardial infarct extension detected by precordial ST segment mapping N Engl J Med 290 123 1974
8 Okinaka S Kumagai H Ebashi S Sugita H Toyokman Y and Fujie Y Serum creatinine phosphokinase activity in progressive muscular dystrophy and neuromuscular disease Arch Neurol. 4 520 1961
9 Hurst J W., Logue R B and Walter P F The clinical recognition and management of coronary atherosclerotic heart disease *in* The heart 4th edition Hurst J W ed New York, 1978 McGraw Hill Book Company Inc p 1195
10 Chung E K Electrocardiography Practical Applications With Vectorial Principles New York 1974 Harper & Row p 157
11 Lown B Tykosinski N Garfeir A and Brooks Ph Sleep and ventricular premature beats Circulation 48 691 1973
12 Rosenbaum M Elzari M V and Lazzari J O The hemiblocks Oldsmar Florida 1970 Tampa Tracings p 71
13 Killip T., and Kimball J T Treatment of myocardial infarction in a coronary care unit A two year experience with 250 patients Am J Cardiol 20 457 1969
14 Frederickson D S A physicians guide to hyperlipidemia Mod Concepts Cardiovasc Dis 41 31 1972
15 DiGirolamo A and Schlant R C Etiology of coronary atherosclerosis *in* The Heart 4th edition Hurst J W ed New York 1978 McGraw Hill Book Company Inc p 1103
16 Hurst J W and Walker H K The Problem Oriented System, New York 1972 Medcom Inc
17 Fleiss J L Statistical methods for rates and proportions, New York 1973 J Wiley & Sons, Inc
18 Nie N H Bent D H H and Hull C H Statistical Package for the Social Sciences, New York 1970 McGraw Hill Book Company Inc
19 Sartwell P E The incubation period and the dynamics of infectious disease Am J Epidemiol. 83 204 1966.
20 Armenian A K and Lilienfeld A M The distribution of incubation period of neoplastic disease Am J Epidemiol. 99 92 1974
21 Stewart C F and Turner K B A note on pericardial involvement in coronary thrombosis AM HEART J 15 232 1938
22 Liem K L. Durrer D Lie K I and Wellens H J J Pericarditis of acute myocardial infarction Lancet 2 1004 1975
23 Guillevin L. and Valere P E Pericarditis in acute myocardial infarction Lancet 1 429 1976
24 Dressler W The post myocardial infarction syndrome Arch Intern Med 103 28 1959
25 Muller J E., Maroko P R and Braunwald E Evaluation of precordial electrocardiographic mapping as a means of assessing changes in myocardial ischemic injury Circulation 52 16 1975
26 Hardarson T., Henning H O Rourke R A Variability reproducibility and applications of precordial ST segment mapping following acute myocardial infarction Circulation 57 1096 1978
27 Zmyslinski, R W Akiyama T., and Biddle T L and Shah P M Natural course of the ST-segment and QRS complex in patients with acute anterior myocardial infarction Am J Cardiol 43 29 1979
28 James, T N Pericarditis and the sinus node Arch Intern Med 110 305 1962
29 Desanctis R W Block P and Hutter A M Tachyarrhythmias in myocardial infarction Circulation 54 681 1972
30 Khan A H Pericarditis of myocardial infarction Review of the literature with case presentation AM HEART J 90 788 1975

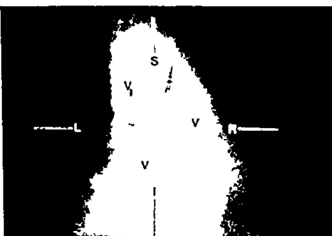


Fig 1 Orifice view of normal aortic valve Quadrant markers S I R and L indicate superior inferior right and left aspects of angiogram as viewed in this and all subsequent illustrations All three sinuses of Valsalva (V_l = left V_r = right V = non-coronary) are clearly seen densely opacified surrounding the triangular appearing orifice and separated from each other by their respective commissures

Table II Classification and findings

Group 1	Two unequal leaflet	
a	Larger leaflet inferior	
	to right	2 cases
	to left	3 cases
b	Larger leaflet superior	
	to left	3 cases
Group 2	Two equal leaflets	
a	Supero-inferior orientation	4 cases
b	Right left orientation	1 case

ration The Group 2 patients (Figs 2 and 5) to the contrary were clearly bicommissural and anatomically and functionally bicuspid An identifiable notch or indentation of a leaflet which we interpret as a raphe was present only in the Group 1a valves (Fig 3) and was uniformly present in the dominant leaflet appearing as a rudimentary separation of this leaflet into the right and non coronary components This raphe is to be distinguished from the commissural fusion resulting in the unicommissural appearance described above

The planimeterized leaflet areas further allowed grouping as described above The ratio of the dominant to non dominant leaflet in all Group 1 valves exceeded 2 1 and was less than 3 1 The Group 2 ratio never exceeded 1 6 1

The orifice appearance was determined by valvular configuration Thus all Group 1 valves exhibited eccentric positions of the orifice Group 1a cases having a superior and generally leftward position (Fig 3) and the Group 1b cases having an inferior and either slight rightward or leftward orientation (Fig 4) The Group 1b valves also appeared to have more complete development of each commissure thus appearing more like the Group 2 valves in this respect and this type of bicuspidization has been indicated by Edwards The Group 2 valves however all had centrally located orifices Group 2a (Fig 2) having a generally horizontal orientation and Group 2b a vertical orientation (Fig 5)

The 13 patients having aortic stenosis unaccompanied by other anomalies comprise all of Group 1 and as well five cases from Group 2 Thus the remaining cases all having additional anomalies had equally bicuspid valves with the exception of the individual with an unequally tricuspid valve

Aortic regurgitation

Aortic regurgitation mild in all instances occurred in four patients in Group 1 whereas only two patients in Group 2 revealed aortic regurgitation one of these patients also had subvalvular aortic stenosis a lesion commonly associated with valvular regurgitation and the other had significant calcific aortic valvular deposits The individual with unequal tricuspid aortic valvular anomaly also exhibited regurgitation

Coronary arterial pattern

The origins of the coronary arteries could be identified in 18 of the orifice view aortograms and a definite pattern could be established in regard to the various valvular configurations Thus in each of the Group 1a valves (Fig 3) the coronary arterial origin appeared essentially normal, the left coronary artery arising from the superior and leftward sinus the right from the rightward aspect of the dominant inferior sinus always to the right of the leaflet raphe This pattern appeared to indicate that the raphe indeed demarcates the absent commissure between the right and non coronary leaflets This pattern of coronary origin did not occur in any of the other valves in the other groups although one of the Group 1b valves had a similar appearance the right coronary artery arising from the right lateral aspect of the sinus of the inferior and non dominant cusp near the commissure and the left coronary ostium appearing at the left lateral

Table I Summary of aortic valve findings

Group	No of patients	Range of peak aortic gradient (average)	Spatial orientation of leaflets[a] (cases)	Leaflet size ratio dominant/non dominant	Raphe position in dominant leaflet	Number and sinus of origin of coronary arteries (cases)	A.R	Orifice location	Other cardiac defects	Surgery
1a	(5)	42-63 (53)	Sup N / Inf D ( ) Sup N / Inf D (3)	2 0-2 6	Inf L (2) Inf R (3)	2 (5) Sup-Inf	2	Eccentric Superior	0	1 (C)
1b	(3)	63-70 (67)	Sup D / Inf N (3)	2 0-3 0	—	1 Sup (1) 2 Sup Inf (1) Undetermined (1)	2	Eccentric Inferior	0	1 (R)
2a	(9)	0-10 (30)	Sup / Inf (9)	1 0-1 6	—	1 Sup (7) 2 Sup (2)	2	Central	2	2 (R)
2b	(1)	17 (17)	L/R (1)	1.3	—	2 Right Left (1)	0	Central	0	—
Tricuspid	(1)	6 (6)	Normal Tricuspid (1)	—	—	1 Right (1)	1	Central	1	—

Abbreviations a = Sup-Inf = Superior Inferior D N = Dominant Non Dominant Leaflet b = where applicable c = less than 2 indicates single origin of both coronary arteries d = AR = aortic regurgitation e = C = commissurotomy f = R = replacement.
Refers to spatial orientation not anatomical configuration

subvalvular aortic stenosis and double outlet right ventricle Four patients have been submitted for surgery one having aortic valvular commissurotomy and three having valve replacement The appearance of the valve in these individuals is available for comparison with the appearance on the orifice view aortogram

Results (Table I)

The appearance of the normal aortic valve on *orifice view aortography is pictured (Fig 1) for* orientation As viewed in this projection the non coronary leaflet occupies the most inferior position with the left coronary leaflet appearing superior and somewhat leftward and the right coronary leaflet appearing somewhat inferior and principally rightward The structure of the congenitally malformed valves was readily evaluated due in part to their tendency to produce a domed appearance during systole This dome seen as a moderately lucent area surrounding the more lucent and often nearly radionegative orifice provided very satisfactory visualization of the *leaflets (Fig 2) and allowed* their measurement by planimetry following image magnification with projection of the selected cine frames

Gross appearance (Table II)

The congenitally malformed values with one exception could be grouped according to gross appearance either as having two leaflets markedly disparate in size (Group 1) or two essentially equal sized leaflets (Group 2) Additionally each group could be subdivided depending upon the spatial orientation of the leaflets Group 1a had the configuration in which the larger (dominant) leaflet was inferior to the smaller (non-dominant) leaflet oriented somewhat to the right in two cases and to the left in three (Fig 3) whereas the three cases comprising Group 1b (Fig 4) had the *dominant leaflet superior and to the left of the* non dominant leaflet Group 2a (Fig 2) exhibited a principally superior inferior leaflet orientation (nine cases) and Group 2b revealed right left orientation (one case) (Fig 5) The sole exception to this classification was a patient having the additional abnormality of double outlet right ventricle in whom the aortic valve was unequally tricuspid with essentially normal leaflet orientation

The Group 1a valves (Fig 3) were all unicommissural Each had one short commissure which allowed partial leaflet separation with systole The other commissure was fused from valve orifice to periphery Thus valves of this type may also be considered as functionally unicuspid although two leaflets are identifiable Those in Group 1b (Fig 4) although similar appeared to have better development of each commissure and thus all tended toward a bicommissural configu

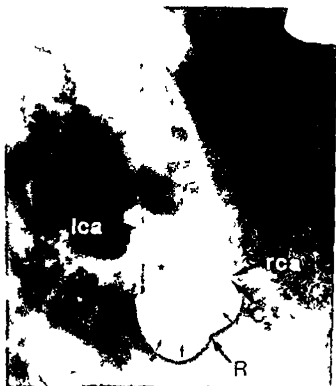


Fig 3 Orifice view of Type Ia valve Peak systolic gradient 47 mm Hg The orifice is marked by asterisk and occupies an eccentric position leftward and superior in the valve incidentally demarcating the superior aspect of the valve dome the inferior margin demarcated by small arrows One commissure (C_1) clearly opens into the orifice the other (C_2) is fused for some distance The two leaflets are obviously of different sizes the dominant inferior leaflet revealing an indentation representing a raphe (arrow R) Left coronary artery (lca) arises from the superior sinus and right coronary artery (rca) from rightward aspect of the inferior sinus This valve is considered a type amenable to simple commissurotomy in view of the long fused commissure

cannot be satisfactorily calculated hemodynamically and a reliable adjunctive measurement in the presence of satisfactory data obtained at the time of left heart catheterization During collection of this data it has become apparent that the technique also allows acquisition of information concerning aortic valvular anatomy in addition to orifice size which may have bearing on the method of surgical management

The aortic valvular anatomic findings by orifice view aortography although similar are not identical to the gross anatomic features reported by Roberts A greater percentage of valves seen angiographically had the appearance of being essentially unicommissural Thus all of the valves included in Group Ia and one from Group Ib had such a configuration comprising 38% of the total excluding the single example of stenotic tricuspid valve Roberts reported a somewhat smaller percentage (20%) of this valve type This difference however may be explained by the fact that most of our patients were children or young adults and this form of aortic valvular malformation has been considered to be the only type inherently stenotic as well as obstructive at birth It should be noted however that four of our patients with no additional cardiovascular malformations had equally bicuspid aortic valves two requiring surgery as adolescents suggesting possible significant stenosis from infancy contrasting somewhat with the report by Edwards that such valves became stenotic principally with the aging process Although each of these valves was essentially without commissural fusion they did not appear to exhibit angiographically the dysplastic appearance reported in this type of valve as a cause of obstruction by Cheitlin and associates[11] and such was also the case in two valves at the time of surgical excision The other five patients had associated malformations and all had trivial or absent aortic valve gradient

Clear cut evidence of a leaflet raphe could be observed angiographically only in those valves representative of Group Ia in which the dominant leaflet appeared to represent fusion of the right and non coronary leaflets although Roberts occasionally found raphes in either or both leaflets regardless of anatomical appearance

Similarly the coronary arterial patterns observed angiographically vary from the findings of Roberts in respect to the Group I cases but are identical in respect to those in Group 2

With these differences from the reported anatomic valvular appearance taken into consideration it seems apparent that orifice view aortography is useful in delineating the anatomy of the malformed aortic valve In four of our patients so far it has quite reliably predicted the anatomy discovered at surgery At present attention is being concentrated upon the appearance of the commissures as regards the presence or absence of identifiable fusion and extent of fusion

The importance of a technique allowing determination of aortic valvular anatomy prior to aortic valve surgery is greatest in childhood and early adult life principally as regards identification of valves amenable to commissurotomy as

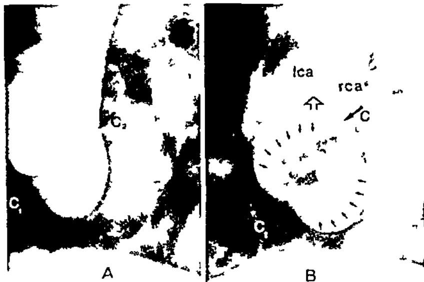


Fig 2 Orifice view of bicuspid aortic valve of Type 2a illustrating features of bicuspidization (see text for description) Peak systolic gradient = 12 mm Hg Coarctation of aorta is associated malformation *A* Valve closed The two commissures are designated by arrows C_1 and C_2 and line of leaflet coaptation may be seen extending from C *B* Valve open The commissures are again identified by arrows C C. The valve orifice presents an elliptical appearance (lucent center) surrounded by a "halo" of lesser lucency (*small arrows*) which represents the valve dome The coronary arteries (*rca* = right *lca* = left) are seen to arise from a single vessel (single left coronary artery) from the superior sinus of Valsalva (*open arrow*)

aspect of the sinus of the dominant cusp The other Group 1b valve revealed both coronary arteries to arise from a single ostium and a trunk located at the right lateral margin of the sinus of the superior dominant leaflet One Group 1b valve could not be analyzed for coronary origin Somewhat similarly (Fig 2) seven of the Group 2a valves had single origin of both coronary arteries from the sinus of the superior cusp and two exhibited the right and left coronary arteries arising separately also from the sinus of the superior cusp The single example of Group 2b had the origin of the right coronary artery from the sinus of the rightward cusp and the left coronary from the sinus of the leftward cusp Finally the individual with unequal tricuspid aortic valve had single origin of both coronary arteries from the sinus of the anatomic right cusp

Anatomic correlation

One patient underwent simple aortic commissurotomy and is the only individual in this series representing Group 1a The angiographic appearance of the valve in this patient indicated a commissure fused for sufficient length to allow for this type of operation At surgery this finding was confirmed and incision was carried out without difficulty The postoperative residual gradient across the aortic valve was 20 mm Hg reduced from 60 mm Hg preoperatively One individual representing Group 1b with angiographic evidence of a nearly continuous slit like orifice without apparent significant commissural fusion required valve replacement Likewise two examples of valves having Group 2a configuration with virtually no commissural fusion also required valve replacement Each of these valves were available in nearly a complete form after surgical removal and each had an appearance similar to the angiographic (Fig 6)

Discussion

The technique of orifice view aortography has been previously shown to be a method by which the size of the aortic orifice could be calculated [2] We have recently demonstrated excellent correlation of the aortic valve area measured by orifice view aortography with that calculated by hydraulic equation concentrating on young individuals with congenital malformations of the aortic valve The sensitivity of the technique is sufficient to allow it to be considered a definitive study for this parameter if for any reason the area



Fig 6 Orifice view of aortic valve Type 2a in *left panel* and appearance of valve at surgical removal, oriented similarly in *right panel* Peak systolic gradient = 102 mm Hg Dome defined by *small arrows* with orifice appearing densely lucent within it Commissures (*arrows* C_1, C_2) fused for short distance Note similar appearance of surgical specimen Commissures were not fused for sufficient length to allow adequate surgical relief as indicated by aortic angiogram

opposed to those requiring replacement If fusion of one or both commissures is observed it is likely that commissurotomy could be performed and provide satisfactory relief of the stenosis The valves with Group 1a configuration stand out prominently in this respect On the other hand if the orifice view aortogram shows that there is little or no fusion of the commissures it is apparent that commissurotomy would not provide satisfactory relief of stenosis and valve replacement would be necessary Avoidance of prosthetic valves all types of which currently in use are fraught with the disadvantage of early failure in the essentially symptom free young patient is preferable to exposing these individuals to the risk of multiple valve replacement and excepting the porcine xenograft the potential risk of thromboembolism Viewing the aortic valve by orifice view projection appears to allow such identification

Summary

Nineteen patients with congenital abnormalities of the aortic valve were studied by orifice view aortography and the anatomic configuration of each valve was determined With one exception all valves were bicuspid The bicuspid aortic valves could be grouped into two distinct categories Group 1 valves had unequal leaflet size and could be further subgrouped depending upon the spatial orientation of the leaflets The commiss ral structure of this type of valve was such th with but two exceptions valvular configurati appeared essentially unicommissural The valv comprising Group 2 exhibited essentially equ sized leaflets and thus are considered equal bicuspid These valves displayed a central orie tation of the orifice and thus are bicommissural contrast to the unicommissural Group 1 valv which all had eccentric orifice position The aort valves examined by this technique exhibited clo similarity to descriptions of valves at the time pathological examination

Orifice view aortography appears to be a repr ducible method of determining the anatomy the aortic valve which can be applied as a preop erative evaluation useful in determining whethe relief of aortic stenosis by aortic commissurotom as opposed to valve replacement is feasible Fou patients undergoing aortic valve surgery on with commissurotomy and three with valv replacement have revealed findings at the time o operation confirmatory of the anatomical config uration of the valve predicted by orifice view aortography

REFERENCES

1 Stein P D Roentgenographic method for measurement of the cross sectional area of the aortic valve Am Heart J 81 62? 1971

2 Stein P D and Sabbah H N Orifice view roentgenog



Fig 4 Orifice view of aortic valve Type 1b Peak systolic gradient = 63 mm Hg Edge of dome demarcated by *small arrows* Each commissure (C_1-C_2) is open for a short distance toward the orifice *(arrow O)* The dominant leaflet is oriented superiorly and the non-dominant is oriented inferiorly The single origin of both coronary arteries (*rca* and *lca*) is identified by arrow *(a)* This valve appears amenable to commissurotomy due to the appearance of significant fusion of each commissure



Fig 5 Orifice view of Type 2b aortic valve Contrast with *Fig 2* Peak systolic gradient = 17 mm Hg The elliptical centrally placed lucent orifice is vertically oriented in the valve dome identified by opposing *solid arrows* Commissure C_1 appears non fused whereas C_2 is fused to valve periphery

The clinical importance of cardioselectivity and lipophilicity in beta blockers

John M Cruickshank DM MRCP*
Macclesfield Cheshire and Manchester England

Ever since Lands in 1967 proposed the existence of two types of beta receptor—beta 1 and beta 2—it has been theoretically desirable for a beta blocker to possess the property of cardioselectivity i e to preferentially block in a competitive fashion the cardiac beta 1 receptor leaving the peripheral beta 2 receptors relatively unhindered A beta blocking agent which is non selective might be expected to confer all the benefits of beta 1 blockade (Table I) but possibly be harmful in blocking beta 2 receptors in for instance (a) bronchial muscle causing bronchoconstriction (b) blood vessels causing vasoconstriction or (c) the liver and muscle prolonging hypoglycemia

Another property of beta blockers the partition coefficient in octanol and water has recently gained prominence A high partition coefficient is associated with lipophilicity and a low coefficient with hydrophilicity Lipophilic beta blockers in general (a) tend to be metabolized by the liver and (b) reach all compartments of the body with relative ease Hydrophilic beta blockers tend (a) to be non metabolized and excreted unchanged by the kidney and (b) reach the deeper compartments of the body such as the brain with relative difficulty

The properties of a beta blocker in particular the properties of cardioselectivity and lipophilici-

Table I Distribution of some of the main beta 1 and beta 2 adrenoceptors

Beta 1	*Beta 2*
Heart	Bronchus
Plasma renin activity (kidney)	Peripheral blood vessel
Intraocular pressure (aqueous humor production)	Uterus
	Insulin (pancreas)
	Lactic acid production
Free fatty acids	Free fatty acids
Glycogenolysis	Glycogenolysis

ty can be predicted from its molecular structure Beta blockers possess either an ethanolamine or an oxypropanolamine side chain (Fig 1) the latter generally conferring greater potency The first beta blockers dichloroisoprenaline (DCI) pronethalol and propranolol (Inderal)* Fig 1 were non selective Subsequently cardioselective oxypropanolamine beta blockers (Fig 2A) were developed which had the common structural feature of an amidic (practolol—Eraldin atenolol—Tenormin acebutolol—Sectral) or other hydrogen binding function (metoprolol—Lopressor or Betaloc) in the paraposition of the benzene ring The amidic functions in particular also reduce the lipophilicity of the molecules Thus atenolol for example is both cardioselective and has low lipophilicity (hydrophilic) That cardioselectivity and hydrophilicity do not necessarily go hand in hand though is shown by the examples of Fig 2B

Beta blockers as a group of drugs are relative to other types of antihypertensive and antiangi-

From the Pharmaceutical Division Imperial Chemical Industries Ltd Macclesfield Cheshire and the Department of Cardiology Wythenshawe Hospital, Manchester England

Received for publication Nov 29 1979
Accepted for publication March 3 1980

Reprint requests Dr J M Cruickshank Medical Dept ICI Ltd Pharmaceuticals Division Mereside Alderley Park Macclesfield Cheshire England

Medical Advisor Imperial Chemical Industries Ltd Macclesfield Cheshire and Clinical Assistant Cardiology Dept Wythenshawe Hospital, Manchester

*Inderal Eraldin and Tenormin are trademarks the property of ICI Limited Sectral Lopressor and Betaloc are trademarks the property of May and Baker Geigy Pharmaceuticals and Astra respectively

0002 8703/80/080160 + 19$01 90/0 © 1980 The C V Mosby Co

raphy for evaluation of the aortic valve Am J Roentgenol 125 847 1975
3 Folger G M Jr Khaja F Anbe D T Sabbah H N and Stein I D Assessment of congenital aortic stenosis by orifice-view aortography (Pt 2) Pediatr Res 13 343 1979
4 Aguilar S Kaulbach M G and Hugenholtz P G Retrograde arterial catheterization of the left ventricle in 398 patients With special reference to aortic valve disease and coarctation of the aorta N Engl J Med 274 312 1966
5 Vlad P Hohn A and Lambert E C Retrograde arterial catheterization of the left heart Experience with 500 infants and children Circulation 29 787 1964
6 Arani D T and Carleton R A Assessment of aortic valvular stenosis from the aortic pressure pulse Circulation 36 30 1967
7 Edwards J E The congenital bicuspid aortic valve Circulation 23 485 1961
8 Roberts W C The structure of the aortic valve in clinically isolated aortic stenosis An autopsy study of 162 patients over 15 years of age Circulation 42 91 1970
9 Roberts W C The congenitally bicuspid aortic valve A study of 85 autopsy cases Am J Cardiol 26 72 1970
10 Edwards J E Calcific aortic stenosis Pathologic Features, Mayo Clin Proc 36 444 1961
11 Cheitlin M D Fenoglio J J McAllister H A Davia J F and De Castro C M Congenital aortic stenosis secondary to dysplasia of congenital bicuspid aortic valves without commissural fusion Am J Cardiol 43 102 1978

Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978 Therefore all manuscripts must be accompanied by the following written statement signed by one author The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C V Mosby Company in the event the work is published The undersigned author warrants that the article is original, is not under consideration by another journal and has not been previously published I sign for and accept responsibility for releasing this material on behalf of any and all co authors Authors will be consulted when possible regarding republication of their material

β-blocker	Log part. coeff octanol/water	Cardioselective	Structure
Sotalol	-0 79	No	CH_3O_2SHN, R
Acebutalol	1 87	Yes	R_1, C, O, CH_3, $NHCOCH_2CH_2CH_3$
Nadolol	0 71	No	R_1, HO, HO
Pindolol	1 75	No	R_1, N, H
Timolol	2 10	No	O, N, N, S, N, OH, OCH_2CHCH_2NHC, CH_3, CH_3, CH_3
Metoprolol	2 15	Yes	R_1, $CH_2CH_2OCH_3$
Oxprenolol	2.18	No	R_1, $OCH_2CH=CH_2$
Alprenolol	2.61	No	R_1, $CH_2CH=CH_2$

Fig 2B Beta blocker partition coefficient in octanol/water cardioselectivity and structure

does not change after chronic administration [1,12] Lipophilic beta blockers by contrast tend to have short plasma half lives The half life of propranolol after a single dose is 2 to 3 hours but appears to lengthen a little after chronic administration [1] This fact is due probably to saturation of the liver enzyme system responsible for the metabolism of propranolol

Clinical implications The possible clinical implications of the above facts are in the areas of dosage interval and predictability of action The former is dealt with later The small between patient variation in peak blood levels of a hydrophilic drug such as atenolol affords a certain predictability of action which is reflected in the narrow dose range for both hypertension and angina [14,15] This contrasts with the large var tion in peak blood levels of the lipophilic li metabolized beta blockers [1] necessitating in vidualisation of dosage However even propra lol might well have a much narrower dose ran than was suggested by earlier studies [17]

2 **Distribution** Within the plasma be blockers bind to proteins in varying degrees T degree of protein binding appears to be indepe dent of the partition coefficient Thus a hyd philic compound such as atenolol is poorly pr tein bound at about 3% [18] Propranolol which highly lipophilic is about 90% protein bound[1] however metoprolol which is also lipophilic only 10% protein bound [2] Now the volume distribution of beta blockers through the vario

β-blocker	Log part. coeff octanol/water	Cardioselective	Structure
Dichlorisoprenaline	3.32	No	Cl, Cl, R
Pronethalol	3.00	No	R
Propranolol	3.65	No	R_1

R CH CH_2NHCH (CH_3)(OH)(CH_3) — Ethanolamine

R_1-OCH_2CHCH_2NHCH (CH_3)(OH)(CH_3) — Oxy-propanolamine

Fig 1 Beta blocker partition coefficient in octanol/water cardioselectivity and structure

nal agents effective and cause few troublesome side effects So in practical terms how real are the supposed advantages of cardioselectivity and how relevant is the property of hydrophilicity? The examples used in this paper for cardioselective agents are atenolol and metoprolol and for the non cardioselective agents propranolol (though not exclusively) The representative of the hydrophilic group of beta blockers (practolol atenolol sotalol and nadolol) will in the main be atenolol and of the lipophilic beta blockers propranolol and metoprolol The subject will fall under two main headings

1. Pharmacokinetics highlighting important differences between hydrophilic and lipophilic beta blockers and the clinical implications, and
2. Pharmacodynamics of cardioselective and non selective beta blockers and the clinical implications

β-blocker	Log part. coeff octanol/water	Cardioselective	Structure
Atenolol	0.23	Yes	R_1, CH_2CONH_2
Practolol	0.79	Yes	R_1, NH_2COCH_3
Acebutolol	1.87	Yes	R_1, O, C, CH_3, $NHCOCH_2CH_2CH_3$
Metoprolol	2.15	Yes	R_1, $CH_2CH_2OCH_3$

Fig 2A Cardioselective beta blockers partition coefficient in octanol/water and structure

Pharmacokinetics—contrasting hydrophilic and lipophilic beta blockers

1 Absorption Hydrophilic drugs have difficulty in crossing cellular membranes and tend to be poorly absorbed from the gut Thus approximately 50% of atenolol[1] and 30% of nadolol are absorbed from the gut However in the case of atenolol at least at a given dose peak blood levels are relatively constant and predictable varying only three to fourfold between patients[3,5] In contrast lipophilic beta blockers such as propranolol[6,7] and metoprolol[8] are well absorbed though there is some twentyfold variation in peak blood levels This variability of peak blood levels is presumably due to the fact that these drugs are metabolized by the liver

Hydrophilic beta blockers tend to have long plasma half lives For example the half life of atenolol after a single dose is 6 to 9 hours[10,11] and

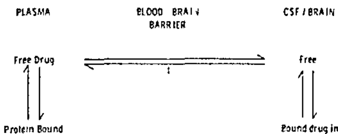


Fig 3 Central nervous system/beta blocker study Beta blocker distribution—blood/cerebrospinal fluid/brain

Table III Accumulation of beta blockers in the lung (dose/mg /kg rat) lung blood concentration ratio (± SEM)*

Beta blocker	*Lung blood concentration ratios*
Propranolol	34 1 ± 6 3
Oxprenolol	18 5 ± 1 1
Metoprolol	11.5 ± 0 5
Acebutolol	5 4 ± 0 4
Practolol	3 0 ± 0 1
Atenolol	1 9 ± 0 2

Reproduced with permission from Hemsworth B A and Street J A

dence of adverse reactions relating to the CNS such as psychosis depression hallucinations nightmares and insomnia [6] Psychotic problems and other CNS side effects arising with lipophilic beta blockers which enter the brain in high concentration[2, 2] disappear or markedly improve when a hydrophilic beta blocker is substituted [9 31] Sixty three such patients suffering CNS side effects on lipid soluble beta blockers were changed to atenolol in 92% the CNS side effects either disappeared or were markedly diminished [30]

3 Excretion Hydrophilic beta blockers tend to be poorly metabolized Thus atenolol is excreted almost totally unchanged by the kidney Ninety to 95% can be recovered in the urine within 48 hours of intravenous administration [1] A small amount 5 to 10% is metabolized by the liver to form a hydroxy metabolite and a glucuronide both of which have only weak pharmacological action [3] In the case of lipophilic beta blockers such as propranolol alprenolol metoprolol and oxprenolol some of the orally administered drug fails to reach the systemic circulation because the drug in the portal vein is taken up and removed by the liver This is termed the first pass effect These drugs are almost wholly metabolized by the liver [33 34] forming metabolites which are weakly pharmacologically active

The plasma half life of a hydrophilic drug like atenolol lengthens with kidney dysfunction,[35] with half lives of 50 hours in patients with very severe dysfunction (glomerular filtration rate 0 to 10 ml /minute) However at glomerular filtration rates) (GFRs) greater than about 35 ml /minute or a serum creatinine less than 2 5 mg % or 300 mmol /L there is no significant accumulation of the drug in the blood [36 3] Lipophilic beta blockers when given to patients with renal failure theoretically should not accumulate However hepatic function and with it the first pass effect appears to be impaired in patients with severe renal failure so that even lipophilic beta blockers like propranolol and metoprolol appear at substantially higher peak blood levels than in patients with normal renal function [34 35] There is also a marked accumulation of metabolites at this time

Elderly (70 years+) compared to young subjects have a decrease (about 40%) in both renal[1] and hepatic function As a drug such as atenolol is virtually unmetabolized by the liver and does not accumulate significantly at GFRs greater than about 35 ml /minute the aging effects upon the kidney and liver should be of little consequence Indeed it has been shown that the pharmacokinetics of a hydrophilic beta blocker (practolol) are similar in both the young and elderly[37] In the elderly liver metabolism of a lipophilic agent such as propranolol is impaired so that blood levels of the parent drug are increased some fourfold with chronic dosing in the elderly [4] With metoprolol there is pronounced inter individual variation in peak plasma levels in the elderly [3]

Clinical implications

a RENAL FAILURE Patients with normal or mild renal dysfunction (GFR greater than about 35 ml /minute or a serum creatinine of less than 2 5 mg % or < 300 mmol /L) do not accumulate (to a significant degree) hydrophilic beta blockers such as atenolol [6 3] thus a normal dosing regimen may be recommended Patients with moderate (GFR 10 to 35 ml /minute or serum creatinine between 2 5 and 5 0 mg % or 300 to 600 mmol /L) and severe (GFR < 10 ml /minute or serum creatinine > 5 0 mg % or > 600 mmol /L) renal dysfunction do accumulate atenolol with blood levels plateauing out in severe cases at about 2 to

Table II Concentration of beta blockers (chronic oral administration) in plasma cerebrospinal fluid (CSF) and brain—in man†

Beta blocker (BB) (dose)	No	Plasma conc ng/ml		CSF conc ng/ml		Brain conc ng/g		Mean plasma/CSF ratio	Mean brain/plasma ratio	Mean brain/CSF ratio
		Indiv values	Mean value	Indiv values	Mean value	Indiv values	Mean value			
Propranolol (80 mg b i d)	3	17 72 370	153	3 3 38	15	830 1 183 5 669	2,561	10	17	171
Metoprolol (100 mg b i d)	1	150	150	130	130	2,108	2 108	1	14	16
Atenolol (100 mg o d)	3	500 300 2,200	1000	72 40 85	66	100 140 160	133	15	0 1	2

= limit of detection
†Reproduced with permission from Cruickshank et al.[11]

body compartments[9] depends upon both lipophilicity and plasma protein binding Thus metoprolol being moderately lipophilic and poorly protein bound has a large volume of distribution = 5 6 L/kg propranolol though having a high lipophilicity is highly protein bound and has a volume of distribution of 3 6 L/kg atenolol although being lowly protein bound is highly hydrophilic and thus has a very low volume of distribution at 0 7 L/kg

Of particular note is the very low concentration of hydrophilic atenolol in the central nervous system (CNS) in rat cat and man[14] This is in contrast to both the lipid soluble propranolol and metoprolol[2, 3] (see Table II and Figs 2*A* and 2*B*) It should be noted that the concentration of the beta blockers in the cerebrospinal fluid (CSF) is a poor predictor of brain concentration

Beta blockers are distributed within the blood/CSF/brain compartments according to the model in Fig 3 Thus in Table II the very low CSF levels of propranolol and metoprolol correspond to the approximate 10% and 90% respectively of free drug in the plasma The very high brain concentration of both propranolol and metoprolol (about 20 times higher than that of atenolol) reflects the high affinity of the brain for these lipophilic agents Early results indicate that oxprenolol another lipophilic beta blocker also appears at higher concentration in brain tissue Distribution of the lipophilic beta blockers within the blood/CSF/brain compartments occurs within *minutes* *In contrast hydrophilic atenolol* crosses the blood brain barrier with difficulty and *equilibration occurs more slowly (Fig 4)* *As the* CSF in man is completely changed about every 10 hours atenolol s concentration may be kept low by means of a continual washout or sink effect[2] Indeed the CSF and brain concentrations seem to settle at about one fifth to one tenth of peak blood values (which occur 2 to 4 hours post dosing) Thus unlike the situation with lipophilic beta blockers with atenolol the brain appears to *be buffered against peak plasma levels*

Another point of interest is the distribution of various beta blockers in lung tissue relative to blood[5] Table III shows a list of lung/blood concentration ratios with lipid soluble drugs appearing in high and highly water soluble drugs in low concentrations in lung tissue The authors offer a possible explanation of cardioselectivity with the water soluble agent (in contrast to the lipid soluble agent) *never attaining a high concentration* in the vicinity of the beta 2 receptor However on this basis sotalol and nadolol would also be selective which is not the case

Clinical implications

a PREDICTABILITY OF ACTION A drug which is poorly protein bound will not be affected by either disease states which alter plasma protein concentrations and ratios or by other drugs which may compete *for protein binding sites* This should contribute to such a drug s predictability in the clinic

b CNS SIDE EFFECTS The low concentration of a hydrophilic drug in the brain relative to lipophilic agents possibly explains the low inci

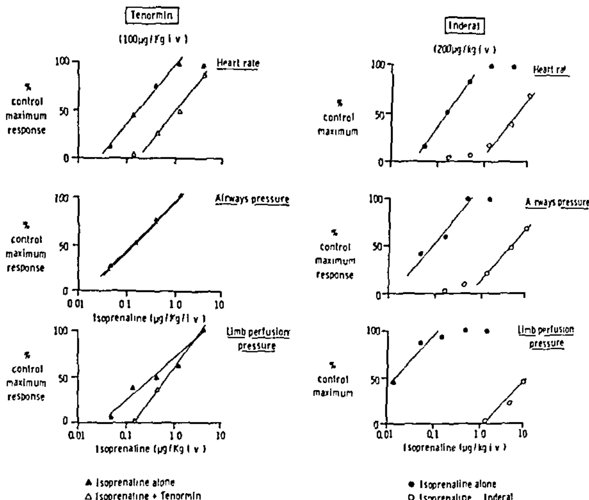


Fig 5 Effect of propranolol and atenolol on heart rate (beta 1) airways pressure (beta 2) and limb perfusion pressure changes resulting from increasing isoprenaline dosage

tions occurring in severe renal failure the cumulative beta blocking effect will be substantial This is a further possible reason for reducing the dose of lipophilic liver metabolized beta blockers in severe renal failure

b THE ELDERLY Compatible with the fact that the pharmacokinetics of hydrophilic beta blockers are similar in the young and the elderly is the observation that the incidence of side effects was the same in young middle and old age groups[45] In contrast lipophilic agents have been reported to produce side effects at a higher incidence in the elderly as compared to the young[4]

Pharmacodynamics

Beta 1 blockade

1 *Cardiovascular*

a HEMODYNAMICS All cardiac beta blockers by definition competitively block beta 1 receptors in the heart with the result that there is a slowing of the heart rate and a decrease in contractility Beta blockade is best demonstrated at the high heart rates associated with moderate to severe exercise as resting heart rates are influenced by vagal tone As stroke volume tends to remain unchanged or possibly slightly increased there is a fall in cardiac output of about 20% at maximal beta blockade The possession of intrinsic sympathomimetic activity (ISA) will tend to be associated with higher heart rates and a lesser fall in cardiac output[47] The fall in cardiac output is initially not accompanied by a fall in blood pressure owing to an alpha mediated reflex increase in peripheral resistance[48] Later probably after only 2 to 3 hours the peripheral resistance falls and is accompanied by a decrease in blood pressure Subjects whose blood pressure does not eventually fall still maintain the initial beta blocker induced increase in peripheral resistance These hemodynamic changes persist for at least one year after starting the beta blocker therapy (atenolol)[5]

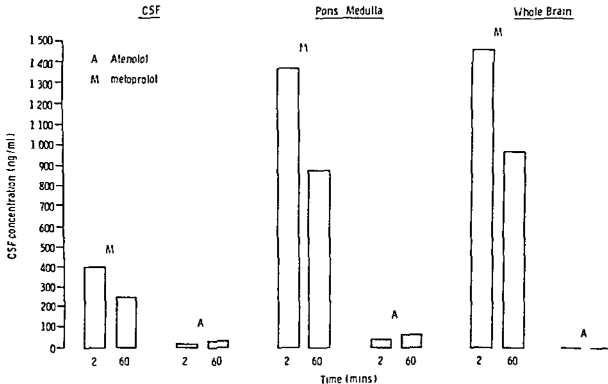


Fig 4 Cerebrospinal fluid/brain concentrations of atenolol and metoprolol Anesthetized cats drugs given intravenouslv/mg /kg

4 weeks[3] Although patients with moderate or severe renal failure tolerate the high blood concentration of atenolol perfectly well blood levels similar to those in the normal therapeutic range are desirable particularly if the benefits of cardioselectivity (which are dose related) are to be retained The conclusions of recent studies on hydrophilic atenolol and renal dysfunction indicated that normal blood levels could be obtained in patients with renal failure and that (1) patients with a GFR of greater than 35 ml/minute should have the normal dose (2) patients with a GFR of 10 to 35 ml/minute should have half the normal dose or the whole dose on alternate days (3) patients with a GFR < 10 ml/minute should have half the normal dose on alternate days and (4) patients on hemodialysis 2 to 3 times a week should be given half the normal daily dose after every hemodialysis (under hospital supervision since marked falls in blood pressure can occur)

Because hepatic function appears to be somewhat impaired in patients with severe renal dysfunction lipophilic beta blockers (propranolol and metoprolol) should also be given in reduced dosage[3] [3] in such cases With the lipophilic beta blockers there is also a marked increase in plasma concentration of liver metabolites[3,9] [0] Although these metabolites have only weak pharmacological activity it seems likely that at the concentra

Table IV Mean cardioselectivity indices (pA cardiac beta 1 receptor pA bronchial beta 2 receptor) in vivo (dog) and in vitro (animal and human)*

Beta blocker	*Mean cardioselectivity indices*	
	In vivo	*In vitro*
Atenolol	1 64	1 71
Practolol	1 59	1 70
Metoprolol	1.54	1 46
Acebutolol	1 40	1.59
Pindolol	0 58	0 30
Propranolol	0 45	0 32

R produced with permission from Harms, H H

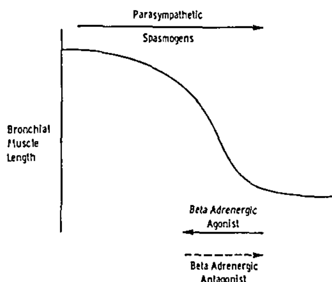


Fig 6 Dose response curve of bronchial muscle

of beta 2 receptors generally has *potentially* detrimental effects It is in these situations that a cardioselective beta blocker might be considered preferable to a non cardioselective beta blocker

Beta 2 blockade

I *Bronchus* Ideally claims for cardioselectivity should be based on data showing that the beta blocker inhibits the beta 1 effects of an agonist upon the heart while having little or no effect upon peripheral beta 2 effects—e g bronchodilation or vasodilatation Such circumstances pertained in the dog model shown in Fig 5 where propranolol produced both beta 1 and beta 2 blockade by shifting the isoprenaline/heart rate and airways pressure dose response curves to the right while atenolol modified only the beta 1 effects Metoprolol behaves in a similar fashion to atenolol[6] Harms using in vitro and in vivo models has presented a table of cardioselective indices (see Table IV) This table is in roughly the reverse order of Hemsworth s table of lung/blood concentration ratios (Table III)

Tattersfield and associates have devised a model in normal volunteers whereby beta 2 specificity or lack of it may be estimated The volunteers were given increasing doses of an inhaled beta 2 stimulant (salbutamol) and the effect upon airways conductance was measured in a whole body plethysmograph All subjects were later exposed to various beta blockers at two dose levels The doses of the various agents were chosen at levels thought to be approximately equipotent and clinically relevant Two hours after administration of the beta blocker the subjects were given salbutamol in increasing doses the effect again being measured in the whole body plethysmograph Dose ratios were estimated the dose ratio being that dose of salbutamol required to produce 50% maximum response (increase in airways conductance) for each drug and dividing this by the dose required to procude 50% response on placebo Table V shows dose ratios and it can be seen that atenolol and practolol caused the least interference with the salbutamol dose response curves and propranolol the most interference Cardioselectivity was illustrated in the case of atenolol by the fact that it caused the greatest fall in exercise heart rate (beta 1) but with practolol the least interference with airways conductance (beta 2) It can be seen that the higher the dose of a beta blocker the more of a beta 2 stimulant (salbutamol) is required to overcome the detrimental effects on airways conductance This confirms that the benefits of cardioselectivity tend to be lost at higher doses[7]

Clinical implications Work by Benson and colleagues[13 14] (Fig 6) has shown that bronchi which are not dependent upon sympathetic drive to maintain their caliber will be little affected by potential spasmogens e g beta 2 blockade Thus results of studies carried out on normal subjects whose bronchi are unstimulated must be regarded as potentially misleading Indeed it is likely that asthmatic subjects who are well with a normal or approaching normal FEV_1 (forced expiratory volume) are able to tolerate beta 2 blockade[15] However patients whose bronchi are dependent upon sympathetic tone to maintain their caliber—i e who fall on the steep part of Benson s dose response curve—are at definite risk from beta 2 blockade A study in a group of such patients[16] (Fig 7) demonstrated two important facts Under circumstances where seven different orally administered beta blockers at clinically relevant doses had produced approximately the same amount of beta 1 blockade (suppression of standing pulse rate and inhibition of the effect of isoprenaline upon the pulse rate) (1) a relatively highly cardioselective beta blocker was *least likely* to cause important branchoconstriction and (2) such a beta blocker (in contrast to non selective agents) almost completely preserved the

ble V Beta blocker dose ratios—modifying effect of beta blockers upon beta 2 stimulated
onchodilatation (airways conductance)*

Beta blocker	Placebo		Practolol		Atenolol		Acebutolol		Labetalol		Propranolol	
e (mg)	–	–	100	200	50	100	100	200	150	300	40	80
in dose ratios	1 00	–	1 11	2 36	1 36	1 94	2.48	3.9	2 10	4 10	23 0	55 9
rcise pulse rates	158	–	127	125	116	104	127	115	135	122	123	116

produced with permission from Tattersfield A E Mackay A D Gribbin H R and Baldwin C J

) BIOLOGICAL HALF LIFE Hydrophilic mainly ally excreted beta blockers tend to have long sma or chemical half lives On the other nd lipophilic mainly liver metabolized beta ckers tend to have short plasma half lives The sma or chemical half life is independent of se contrasting with the biological or pharma ogical half life which is dose dependent For mple a beta blocker such as atenolol with a g chemical half life (6 to 9 hours) when ministered in a relatively low dose of 50 mg e rise to beta blockade 24 hours after the dose ich was about 30% of maximum (decrease in art rate three hours after the dose) By doub g the dose it was possible to achieve about 70% maximum blockade 24 hours after the dose

e same principle applies to the beta blockers h short chemical half lives However if biolog l effect is required over a 24 hour period an ent with a short chemical half life will need to administered at high dosage relative to an ent with a long chemical half life even though th agents might be equipotent milligram for lligram in producing maximal beta blockade at 2 to 3 hours post dose For example metopro with a short chemical half life and atenolol h a longer chemical half life are considered to equipotent milligram for milligram in sup essing exercise heart rate or systolic blood ssure 2 to 3 hours after dosing Whereas enolol (dose 100 mg) produced a substantial crease in both exercise heart rate and systolic ood pressure 24 hours post dosing little or no ect remained 12 to 24 hours after the same dose metoprolol[5 5] However equipotency of effect er 24 hours could be achieved either by tripling e single dose of metoprolol or by giving the dose ice daily[5]

c ELECTROPHYSIOLOGY Both cardioselective enolol and non selective propranolol have the me effect on the sinus and AV nodes Both ugs equally slow the sinus rate prolong sinoa ial and AV nodal conduction time (A H in His ndle ECG) and prolong the effective refractory period of the A V node[56 5] neither the conduction time within the atrium the His Bundle and ventricle nor the refractory periods of these compartments are altered by atenolol or propranolol However one study indicated that atenolol but not propranolol increased atrail refractoriness[5]

2 *Renin* Renin release is probably primarily a beta 1 effect thus both cardioselective and non cardioselective beta blockers equally suppress plasma renin activity (PRA)[1 5 59] Earlier claims that atenolol had no effect on the renin angiotensin system[6] results from measurements on plasma renin concentration (not PRA) which was not affected by atenolol

3 *Intraocular pressure* A decrease in production of aqueous humor arises after beta 1 blockade[1] Thus both non selective and cardioselective beta blockers lower intraocular pressure with equal facility

4 *Anxiety/tremor* The peripheral signs of both anxiety and thyrotoxicosis[65] seem to be blocked equally well by both non selective propranolol and cardioselective atenolol

Clinical implications Clinical states which benefit primarily from blockade of beta 1 receptors such as angina dysrhythmias glaucoma high renin situations and possibly anxiety and thyrotoxicosis will be equally affected by both cardioselective and non cardioselective agents In hypertension and indeed angina it should be possible to administer a hydrophilic beta blocker on a once daily basis at relatively low dosage This should hopefully help foster good patient compliance in adhering to the therapy Moreover the benefits of cardioselectivity will still be maintained at low dosage (see below) which will not be the case if as in the case of a cardioselective lipophilic agent with a short clinical or plasma half life dosage is increased in order to achieve 24 hour effect

In conditions that possibly benefit from beta 2 blockade (migraine)[67] cardioselective beta blockers may have no useful action However blockade

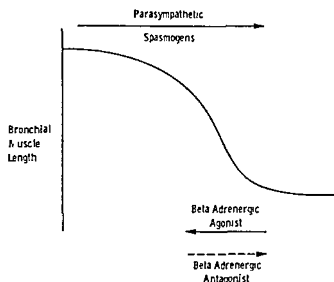


Fig 6 Dose response curve of bronchial muscle

of beta 2 receptors generally has *potentially* detrimental effects It is in these situations that a cardioselective beta blocker might be considered preferable to a non cardioselective beta blocker

Beta 2 blockade

I *Bronchus* Ideally claims for cardioselectivity should be based on data showing that the beta blocker inhibits the beta 1 effects of an agonist upon the heart while having little or no effect upon peripheral beta 2 effects—e g bronchodilation or vasodilatation Such circumstances pertained in the dog model shown in Fig 5 where propranolol produced both beta 1 and beta 2 blockade by shifting the isoprenaline/heart rate and airways pressure dose response curves to the right while atenolol modified only the beta 1 effects Metoprolol behaves in a similar fashion to atenolol[6] Harms [9] using in vitro and in vivo models has presented a table of cardioselective indices (see Table IV) This table is in roughly the reverse order of Hemsworth s table of lung/blood concentration ratios (Table III)

Tattersfield and associates[7] have devised a model in normal volunteers whereby beta 2 specificity or lack of it may be estimated The volunteers were given increasing doses of an inhaled beta 2 stimulant (salbutamol) and the effect upon airways conductance was measured in a whole body plethysmograph All subjects were later exposed to various beta blockers at two dose levels The doses of the various agents were chosen at levels thought to be approximately equipotent and clinically relevant Two hours after administration of the beta blocker the subjects were given salbutamol in increasing doses the effect again being measured in the whole body plethysmograph Dose ratios were estimated the dose ratio being that dose of salbutamol required to produce 50% maximum response (increase in airways conductance) for each drug and dividing this by the dose required to procude 50% response on placebo Table V shows dose ratios and it can be seen that atenolol and practolol caused the least interference with the salbutamol dose response curves and propranolol the most interference Cardioselectivity was illustrated in the case of atenolol by the fact that it caused the greatest fall in exercise heart rate (beta 1) but with practolol the least interference with airways conductance (beta 2) It can be seen that the higher the dose of a beta blocker the more of a beta 2 stimulant (salbutamol) is required to overcome the detrimental effects on airways conductance This confirms that the benefits of cardioselectivity tend to be lost at higher doses[7]

Clinical implications Work by Benson and colleagues[13, 14] (Fig 6) has shown that bronchi which are not dependent upon sympathetic drive to maintain their caliber will be little affected by potential spasmogens e g beta 2 blockade Thus, results of studies carried out on normal subjects whose bronchi are unstimulated must be regarded as potentially misleading Indeed it is likely that asthmatic subjects who are well with a normal or approaching normal FEV_1 (forced expiratory volume) are able to tolerate beta 2 blockade[15] However patients whose bronchi are dependent upon sympathetic tone to maintain their caliber—i e who fall on the steep part of Benson s dose response curve—are at definite risk from beta 2 blockade A study in a group of such patients[7] (Fig 7) demonstrated two important facts Under circumstances where seven different orally administered beta blockers at clinically relevant doses had produced approximately the same amount of beta 1 blockade (suppression of standing pulse rate and inhibition of the effect of isoprenaline upon the pulse rate) (1) a relatively highly cardioselective beta blocker was least likely to cause important branchoconstriction and (2) such a beta blocker (in contrast to non selective agents) almost completely preserved the

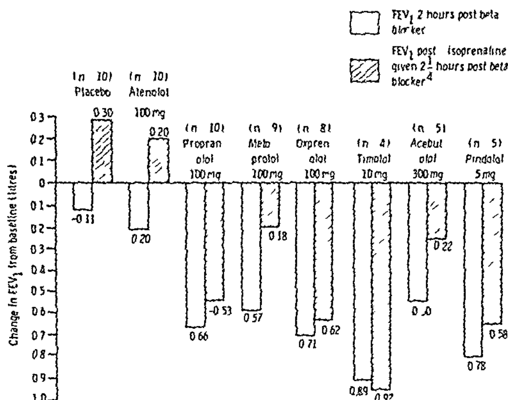


Fig 7 Effect of beta blocker and isoprenaline upon forced expiratory volume (FEV) in 10 responding (labile) asthmatic patients

2 bronchodilator action of isoprenaline should be emphasized that an asthmatic nt who is well and who falls on the flat on of Benson s dose response curve might be from beta 2 blockade at a different point in This fact is well illustrated (Benson person inication) by the asthmatic patient who n his FEV was 4 2 liters tolerated proprano mg well with no change in FEV However al months later (on no therapy) when he was ezy with an FEV of 2 9 liters he was unable olerate propranolol 80 mg propranolol sed his FEV, to fall to 1 7 liters and precipi d severe asthma It is thus recommended that on selective beta blocker should never be ed to a patient with reversible airways ction

- s cardioselective beta blockers like atenolol metoprolol do not confer absolute safety re will be occasional asthmatic patients who ond in an adverse way and it is recommended that atenolol and metoprolol should be prescribed alongside a beta 2 stimulant such as isoprenaline salbutamol or terbutaline in symptomatic asthmatic patients Another point worth emphasizing again is that cardioselectivity is a dose dependent property Thus the dose of a cardioselective agent should be kept as low as possible in patients at risk otherwise the advantages of cardioselectivity will be diminished [18]

Finally one ought to be aware of the possible role of metabolites in determining the cardioselective profile of a beta blocker Thus the acetyl metabolite of acebutolol which appears in the plasma at higher concentrations than its parent drug [9] is probably less cardioselective than acebutolol itself [9]

II *Peripheral blood vessels* Fig 5 showed that the non selective beta blocker not only competitively inhibited the beta 2 associated increase in bronchial airflow but also competitively inhibited the beta 2 associated increase in peripheral

function during treatment with a non selective compared to a cardioselective beta blocking drug this may be of importance in patients with renal disease

It would thus seem reasonable to prescribe a cardioselective agent to patients with renal dysfunction who require beta blocker therapy However a non selective beta blocker (nadolol)[111, 112] has been claimed to actually increase renal blood flow Such a claim is surprising and needs confirmation

6 MIGRAINE Non selective propranolol is almost certainly effective in treating migraine[8] Evidence to date (Behan personal communication) suggests that a cardioselective beta blocker is probably not effective in treating migraine However well controlled studies are required before this suspicion becomes fact

III *Metabolic*

a INSULIN SECRETION Resting insulin levels seem to be unaffected by beta blockers[115] However stimulated insulin secretion[116] is markedly suppressed by non selective beta blockers such as propranolol and only slightly suppressed by atenolol

b GLYCOGENOLYSIS AND GLUCONEOGENESIS It has been shown[1, 11] that the return of blood sugar to normal after insulin induced hypoglycemia was delayed by non selective but not by cardioselective beta blockade There are two possible explanations of this (1) that a beta 2 aspect of glycogenolysis is blocked by the non selective and not by the cardioselective beta blocker thus impairing the liver s ability to replenish the blood sugar and (2) non selective but not cardioselective beta blockers block lactic acid and glycerol (inhibits lipolysis) release from muscle[11] and thus the liver is denied substrate for gluconeogenesis

c. FREE FATTY ACIDS (FFAS) Basal FFA blood levels are suppressed equally by both selective and non selective beta blockers[5] although this effect appears to diminish in time However a stress induced increa e in FFAs tends to be better suppressed by a non selective beta blocker[11, 9] suggesting a de[illegible] beta 2 component

Clinical imp[illegible]

a. DIABETES [illegible] basal insulin secretion is unaffected by [illegible] blockers stimulated insulin secretion is [illegible]edly suppressed by non selective beta blo[illegible] This latter occurrence might explain the observations of Waal Manning[10] in which some patients while on propranolol had chemical diabetes but on metoprolol they had a normal glucose tolerance test These observations have not been confirmed in another study[116] in which in fact the post propranolol blood sugar tended to be somewhat lower than after a cardioselective drug (atenolol)

The importance of hypoglycemia associated with propranolol therapy has probably been much exaggerated[1] and most diabetic patients may be given this drug with safety[12] However hypoglycemia is undoubtedly a rare but important side effect with non selective beta blockade[121] particularly for diabetic patients on insulin[124, 125] fasting subjects (particularly children)[126, 127] post myocardial infarction patients[1] and possibly in patients undergoing hemodialysis[1] Moreover *the speed of* recovery of the blood sugar to normal is impeded by non selective beta blockers in contrast to cardioselective agents[11, 119] Interestingly hypoglycemic symptoms such as sweating and pallor appear to be unaffected by beta blockers the tachycardia is however suppressed more so by non selective than by cardioselective agents These observations have led these authors and others[130] to conclude that for the insulin-dependent diabetic patient requiring a beta blocker a cardioselective agent would be preferable

b FREE FATTY ACIDS It has been suggested by some that increased FFA levels in the post infarction period might be causing important dysrhythmias[131] However in a randomized study involving oral administration of either atenolol, propranolol or placebo[32] within hours of myocardial infarction (and continuing for one year) 24 hour ECG taping showed that the number of important ventricular dysrhythmias was the same for both agents (and indeed differed but little from placebo) It would thus appear likely that a non selective beta blocker will not confer an advantage in this area in terms of post infarction dysrhythmia prevention or indeed in dysrhythmias not associated with myocardial infarction[133]

Suggestions that high plasma FFA levels will increase atheroma formation and that a non selective beta blocker (in contrast to a selective agent) will hinder this process are entirely speculative

odilation might theoretically be expected to luce a lower blood pressure than a beta ker that does not

Resting blood pressure (supine and stand

ı

Iost studies[2,100] in which orally administered nolol has been compared with non selective a blockers on a crossover basis have indicated t atenolol is a superior antihypertensive agent ix of these studies atenolol was given in e daily doses and the non selective agent was *n either once[97] twice or four times daily*

In the remaining three studies both nolol and the non selective agents were given a twice daily basis Metoprolol also claims a ilar advantage However other studies em ying a crossover design and twice daily dosing e indicated that little difference exists between the antihypertensive effect of selective and ı selective agents On balance it is likely that a dioselective beta blocker is slightly more ef tive in lowering diastolic blood pressure

Exercise blood pressure

Dynamic It has been indicated that cardiose tive beta blockers administered on a crossover is either intravenously[1] or orally are erior to non selective agents in lowering the od pressure associated with dynamic exer [97,10,104] However more well conducted stud are required before these claims of atenolol l metoprolol can be regarded as proven

sometric Claims have also been made that lly administered cardioselective beta blockers more effective in preventing the rise in blood ssure associated with handgrip exercise wever others have not confirmed this and question must remain unanswered at pres

Stress hypertension

Iental Claims have been made[1] that orally ministered cardioselective agents are more ective than non selective agents in preventing rise in blood pressure associated with mental ess But confirmation of these results has not n forthcoming[107] and the question must nain open One study[8] has shown that non ective blockade (intravenous propranolol) used a diastolic pressor effect during mental ess

Insulin *treated diabetic During insulin hypo* cemia cardiovascular changes occur which are nilar to those occurring after adrenaline infu sion[109] Intravenous administration of a non selective beta blocker under these conditions blocks not only beta 1 receptors but also beta 2 vasodilator receptors with the result that a dia stolic pressor response of some 10 to 15 mm Hg occurs In contrast the pressor response is absent or diminished with a cardioselective beta blocker (metoprolol) administered either intrave nously[11] or orally[111] Thus for insulin treated diabetic patients requiring a beta blocker — the choice of a cardioselective agent is possibly pref *erable*

Smoking The act of smoking as with insulin induced hypoglycemia is associated with in creased adrenaline secretion tachycardia and an increase in both systolic and diastolic blood pressure (Fig 8) Intravenous administration of a non selective beta blocker during smoking did not diminish the systolic rise in blood pressure and caused a marked diastolic pressor response (15 to 20 mm Hg) In contrast cardioselective atenolol lowered the systolic blood pressure and did not cause a diastolic pressor response If these obser vations are confirmed in chronic oral studies there could be important implications in the choice of agent for the patient who insists on smoking and who also requires beta blocker ther apy

4 ANGINA Parratt and Marshall s work in animals has suggested that beta blockers with ISA and/or cardioselectivity in contrast to non selective beta blockers, are less likely to embarrass coronary hemodynamics Such a property might theoretically be beneficial to the anginal patient Astrom and Vallin have in fact claimed such an advantage for atenolol (5 mg intravenously) over propranolol (5 mg intravenously) but explain this on the basis that atenolol was asso ciated with a lesser rise in exercise blood pressure and thus lessened the afterload on the heart However other studies that have compared oral atenolol with propranolol and oxprenolol on a randomized crossover basis have shown no difference in antianginal effect

5 RENAL FUNCTION The minimal effect of cardioselective relative to non selective beta blockers upon effective renal plasma flow and creatinine clearance has led one group to conclude that treatment with atenolol would *appear not to cause significant reduction* of renal function and another investigator[4] to declare that he found a greater deterioration in renal

selective in contrast to a non selective beta blocker (with no ISA) Some patients with intermittent claudication thus will have a greater exercise tolerance with a cardioselective beta blocker

4 Antihypertensive control Because cardioselective beta blockers preserve beta 2 vasodilator action they are possibly slightly more effective antihypertensive agents than are non selective bete blockers

5 Stress hypertension Hypertension associated with increased adrenaline secretion—e g insulin induced hypoglycemia smoking and possibly mental stress is exacerbated (diastolic pressor effect) by a non selective beta blocker This is not the case with a cardioselective beta blocker

6 Renal function Renal function (effective renal plasma flow and creatinine clearance) is less compromised on cardioselective compared to non selective beta blockers (? nadolol excepted) This fact might be of importance to patients with already impaired renal function

7 Migraine Non selective propranolol is an effective prophylactic drug for migraine It is doubtful if cardioselective beta blockers will be effective

8 Blood sugar The majority of diabetic patients tolerate propranolol well The return of blood sugar to normal after insulin induced hypoglycemia is dependent to some extent on beta 2 receptor integrity (glycogenolysis and gluconeogenesis) A non selective beta blocker in contrast to a cardioselective beta blocker prolongs the hypoglycemic period Thus for patients at risk from hypoglycemia who require beta blocker therapy a cardioselective agent is probably preferable

REFERENCES

1 McAinsh J Clinical pharmacokinetics of atenolol Postgrad Med J 53 74 1977

2 Dreyfuss J Brannick J I Vukovich R A Shaw J M and Willard D A Metabolic studies in patients with nadolol oral and intravenous administration J Clin Pharmac 1 17 300 1977

3 Brown H C Carruthers S G Johnston G O Kelly J G McAinsh J McDevitt D G and Shanks R Clinical pharmacological observations on atenolol a beta adrenoceptor blocker Clin Pharmacol Ther 20 524 1976

4 Fitzgerald J D Ruffin R Smedstad R Roberts R and McAinsh J Studies on the pharmacokinetics and pharmacodynamics of atenolol in man Eur J Clin Pharmacol 13 81 1978

5 McAinsh J Review of pharmacokinetics of Tenormin R Soc Med International Congress and Symposium Series 19 Academic Press London and New York 1979

6 Chidsey C A Marselli P Bianchetti C Morganti A Leonetti G and Zanchetti A Studies of absorption and removal of propranolol in hypertensive patients during therapy Circulation 52 313 1975

7 Shand D G Pharmacokinetic properties of the beta adrenergic receptor blocking drugs Drugs 7 39 1974

8 von Bahr C Collste P Frisk Holmberg M Haglund K Jorfelt L Orme M Ostman J and Sjoqvist F Plasma levels and effects of metoprolol on blood pressure adrenergic beta blockade and plasma renin activity in essential hypertension Clin Pharmacol Ther 20 130 1976

9 Johnsson G and Regardh C C Clinical pharmacokinetics of beta adrenoceptor blocking drugs Clinical Pharmacokinetics Adis Press Australasia PTY Ltd 1 233 1976

10 Shanks R Carruthers S G Kelly J G and McDevitt D G Correlation of reduction of exercise heart rate with blood levels of atenolol after oral and intravenous administration Postgrad Med J 53 0 1977

11 McDevitt D G Johnston G D Kelly J G and Shanks R G Investigation of chronic dosing regimen of atenolol Postgrad Med J 53 9 1977

12 Hawksworth G M, Jeffers T A Petrie J C Webster J and Barber H E Withdrawal of long terms therapy with atenolol in hypertensive patients (Abstr) VIIth International Congress of Pharmacology Paris July 1978

13 Evans C H and Shand D G The disposition of propranolol Independent variation in steady state circulating drug concentrations and half life as a result of plasma binding in man Clin Pharmacol Ther 14 494 1973

14 Douglas Jones A P and Cruickshank J M Once daily dosing with atenolol in patients with mild or moderate hypertension Br Med J 1 990 1976

15 Jackson G, Harry J D Robinson C Kitson D and Jewitt D E Comparison of atenolol with propranolol in the treatment of angina pectoris with special reference to once daily administration of atenolol Br Heart J 40 998 1978

16 Shand D C Pharmacokinetic properties of the beta adrenoceptor blocking drugs Cardiovascular Drug Vol 2 Beta adrenoceptor blocking drugs Adis Press Australasia PTY Ltd 1977 p 41 54

17 Galloway D B Glover S C Hendry W G Logie A W Petrie J C Smith M C Lewis J A and Simpson W T Propranolol in hypertension a dose response study Br Med J 2 140 1976

18 Barber H E Hawksworth G M Kitteringham N R Petersen J Petrie J C and Swann J M Protein binding of atenolol and propranolol to human serum albumin and in human plasma Br J Clin Pharmacol 6 446p 1978

19 Evans G H Nies A S and Shand D G The disposition of propranolol III Decreased half life and volume of distribution as a result of plasma binding in man monkey dog and rat J Pharmacol Exp Ther 186 114 1973

20 Johansson K A Appelgren C Borg K O and Flofsson R Binding of two adrenergic beta receptor antagonists alprenolol and H93/26 to human serum proteins Acta Pharm Suec 11 333 1974

21 Abel M J Longshaw S and Reeves F Atenolol and the blood brain barrier of the rat a comparison with

Uterus Animal studies suggest that beta 2 ... increases the frequency and strength of ... of the gravid uterus[134]

... AL IMPLICATIONS Most studies[135 13] ...ate that beta blockers (propranolol and ...prenolol) may be given to the pregnant female ... harm to mother of child Indeed one ...dy[137] indicated a superiority of the beta block (oxprenolol) over methyldopa the former ...g associated with heavier placentas and birth ... Some[139 141] suggest that beta blockers ...ght harm the foetus However the fears that a ...n selective beta blocker might precipitate pre...ature contractions and miscarriage have not borne out

Cardioselective beta blockers tend as a group be hydrophilic However hydrophilicity is not essential factor for the expression of cardiose... ...kewise non selective beta blockers are ...lly lipophilic but lipophilicity is not an ... factor for expression of non selectivity ...ugh beta blockers as a group are effective and ...use few troublesome side effects an agent ... is cardioselective hydrophilic and non ...olized has in contrast to one which is ...n selective lipid soluble and metabolized sev... advantages in certain clinical areas

...inetic (hydrophilicity versus lipo...hilicity)

1 Blood levels and length of action Consistent ...tween patient peak blood levels (only ... to fourfold variation compared to twenty ...d with liver metabolized agents like proprano... and metoprolol) render a hydrophilic beta ... such as atenolol a very predictable drug the clinical situation and are probably contrib...ing to its narrow dose range Being unmetabo...l and renal excreted hydrophilic beta block... have a long biological action which enables a dose to be given on a once daily basis ... in 24 hour cover for both hypertension angina

2 The brain In man very little atenolol (hy...) enters the brain (about one twentieth the concentration of a lipophilic beta blocker) has a brain/blood ratio of approximately 0 1 1 ...d to 17 1 and 14 1 with propranolol and ...prolol (both lipophilic) respectively This ...ssibly accounts for (1) the low incidence of side effects relating to the CNS and (2) the disappearance of CNS side effects on changing from lipophilic beta blockers to atenolol

3 The kidney Hydrophilic beta blockers such as atenolol and nadolol are excreted virtually unmetabolized by the kidney However in the case of atenolol at glomerular filtration rates above 35 ml /minute (or serum creatinine of < 2 5 mg % or 300 mmol /L) there is no significant drug accumulation and the normal dose may be given Significant accumulation occurs in moderate to severe renal failure so that in order to achieve optimal therapeutic blood levels at glomerular filtration rates between 10 and 35 ml / minute (serum creatinine 2 5 to 5 0 mg % or 300 to 600 mmol /L) the daily dose should be halved and at glomerular filtration rates less than 10 ml /minute (serum creatinine > 5 0 mg % or 600 mmol /L) half the daily dose should be given on alternate days With lipophilic liver metabolized beta blockers like propranolol and metoprolol there is likewise a tendency for increased blood levels in severe renal failure (due to the accompanying liver dysfunction) These higher blood levels plus a marked accumulation of metabolites are an indication for dosage reduction

4 The elderly The elderly handle and tolerate hydrophilic beta blockers in a similar fashion to younger subjects Due to the liver dysfunction associated with aging (hepatic blood flow decreased 40 to 50% in the 70 years old subjects) lipophilic beta blockers like propranolol achieve blood levels in the elderly up to fourfold higher than in younger subjects this may account for the possible higher incidence of side effects in the elderly

Pharmacodynamic (cardioselectivity versus non selectivity)

1 Asthma At low doses atenolol and metoprolol are highly cardioselective (cardioselectivity is dose related) and are the beta blockers probably least likely to cause a fall in forced expiratory volume (FEV_1) in patients with reversible airways obstruction Also unlike non selective beta blockers they preserve the bronchodilator action of a beta 2 stimulant such as isoprenaline

2 Cold extremities Cold extremities can occur with all beta blockers but the temperature change is minimal on a cardioselective agent

3 Peripheral blood flow Peripheral blood flow during exercise is less compromised with a cardio

60 Amery A., Billiet L. and Fagard R Beta receptors and renin release N Engl J Med 290 284 1974
61 Yablonski, M E., Zimmerman T J., Waltman S R., and Becker B A fluorophotometric study of the effects of topical timolol on aqueous humor dynamics, Exp Eye Res. 27 135 1978
62 Phillips, C I., Howitt G., and Rowlands D J Propranolol as occular hypotensive agent, Br J Ophthalmol. 51 222, 1967
63 Elliot M J., Cullen P M., and Phillips, C I Occular hypotensive effect of atenolol (Tenormin ICI) Br J Ophthalmol. 59 296 1975
64 Clayton A B Harvey P G., and Betts, T A The psychomotor effects of atenolol and other antihyperten sive agents Postgrad Med. J 53(3) 157 1977
65 McDevitt D G., and Nelson J K Comparative trial of atenolol and propranolol in hyperthyroidism Br J Clin. Pharmacol. 6 233 1978
66 Nilsson, O R., Karlberg B E., Kagedal B Tegler L and Almqvist S Non-selective and selective beta 1 adrenoceptor blocking agents in the treatment of hyper thyroidism Acta Med Scand. 206 21 1979
67 Wideroe T E., and Vigander T Propranolol in the treatment of migraine Br Med J 2 699 1974
68 Wale J L., and Fitzgerald, J D Assessment and clinical implications of cardioselectivity Proc R Soc. Med. 70 45 1977
69 Johnsson, G Use of beta adrenoreceptor blockers in combination with beta timulators in patients with obstructive lung disease Drug 11(Suppl. 1) 171 1976
70 Harms, H H Cardioselective beta adrenoceptor block ing agents Human and animal studies in vitro and in vivo Amsterdam 1977 Enroprint BV Rijswijk pp 1790
71 Tattersfield A E., Mackay A. D., Gribbin H R., and Baldwin C J How cardioselective are the new beta blocking drugs? (Abstr) VIth Scientific Meeting of the International Society of Hypertension Gothenburg June 1979
72 Singh, B N., Nisbet H D., Harris, E A., and Whitlock, R. M. A comparison of the actions of ICI 66 082 and propranolol on cardiac and peripheral beta adrenoceptors, Eur J Pharmacol. 34 75 1975
73 Benson, M K and Graft, P D Bronchial reactivity interaction between stimulation and inhaled histamine J Appl. Physiol. 43 643 1977
74 Benson M K Cardioselectivity studies, Proc. R Soc. Med. 70 48 1977
75 Benson M K., Berrill, W T., Cruickshank, J M., and Sterling, G S A comparison of four beta adrenoceptor antagonists in patients with asthma, Br J Clin Phar macol. 5 415 1978
76 Decalmer P B., Chatterjee S S., Cruickshank J M., Benson, M K and Sterling, G M Beta blockers and asthma Br Heart J 40 184 1978
77 Zacharias, F J., Cuthbertson, P J., Prestt J., Cowen K. J., Johnson T B Thompson J Vickers, J., Simpson W T and Tuson R Atenolol in hypertension a study of long term therapy Postgrad. Med J 53(3) 102 1977
78 Formgren, H The effect of metoprolol and practolol on lung function and blood pressure in hypertensive asth matics. Br J Clin Pharmacol 3 1007 1976
79 Winkle R A Meffin P J Ricks, W B and Harrison D C Acebutolol metabolite plasma concentration during chronic oral therapy Br J Clin. Pharmacol. 4 519 19
80 Collins R F Pharmacocinetique de lacebutolol Nouv Presse Med 4 3223 1975
81 Warren D J McSorley P., and Naik R.B Effects of beta adrenergic blocking drugs on peripheral blood flow (Abstr) VIIIth World Congress of Cardiology Tokyo September 1978
82 Bonelli, J., Hortnagel, H., Brücke Th., Magometschnigg D., Lochs, H., and Kaik G Effect of calculation stress on hemodynamics and plasma catecholamines before and after beta blockade with propranolol and mepindolol sulphate Eur J Clin Pharmacol. 15 1 1979
83 von Euler U S., and Luft R. Effect of insulin on urinary excretion of adrenalin and noradrenalin Metabolism 1 528-532 1952
84 Trap-Jensen J., Carlsen J E., Svendsen T L., and Christensen N J Cardiovascular and adrenergic effects of cigarette smoking during immediate non selective and selective beta adrenoceptor blockade in humans, Eur J Clin. Invest 9 1979 (In press)
85 Parratt J R., and Marshall R. J Beta adrenoceptor blocking drugs in acute experimental myocardial ischaemia (Abstr) VIIIth World Congress of Cardiology Tokyo September 1978
86 Simonsen S Effect of atenolol (ICI 66 082) on coronary haemodynamics in man Br Heart J 39 1210 1977
87 Lichtlen P R., Engel, H J and Hundeshagen, H. Regional myocardial blood flow in normal and post-stenotic areas of nitroglycerin beta blockade (atenolol) coronary dilatation (dipyridamole) and calcium antag nonism (nifedipine) Herz 2 81 1977
88 Waal Manning H J., and Bolli P Cardioselective beta blockade and renal function Br Med J 1 1089 1979
89 Wilkinson R Beta blockers, blood sugar control and renal function Br Med J 1 617 19 9
90 Middlemiss, D N., Blakeborough L., and Leather S R. Direct evidence for an interaction of beta adrenergic blockers with the 5HT receptor Nature 276 29 1977
91 Marshall A J., Roberts, C J and Barritt, D W Raynaud s phenomenon as side effect of beta blockers in hypertension Br Med. J 1 1498 19 6
92 Zacharias F J., and Cowan K J Comparison of propranolol and atenolol in hypertension, Postgrad. Med J 53 111 1977
93 Epstein S E., and Lubbe W F Effects of propranolol and atenolol on blood pressure and plasma renin activ ity in patients with moderate hypertension, S Afr Med J 52 875 1977
94 Harvald B Clinical report on 'Tenormin —A within patient comparison of "Tenormin" and Inderal" in the treatment of arterial hypertension Symposium New Perspectives in the Treatment with Beta Receptor Blocking Drugs Scanticon, Denmark, January 19 8
95 Turner A. S., and Brocklehurst J E. Comparison of the efficacy of a single daily dose of acebutolol and atenolol in the treatment of arterial hypertension, Med. J Aust 1 625 1979
96 Frewin D B., Harman, A. W., Penhall, R. K., and Priestly B G A comparison of the efficacy of atenolol with either propranolol or pindolol in the management of hypertension (Submitted for publication)
97 Wilcox, R G Randomised study of six beta blockers and a thiazide diuretic in essential hypertension, Br Med J 2 383 1978
98 Wilcox, R G Beta blockers in the treatment of hypertension Br Med J 2 1060 19 8
99 England, J D F., Hua, A. S P., and Shaw J Beta

propranolol Imperial Chemical Industries Limited Pharmaceuticals Division Safety of Medicines Department February 1978

van Zwieten P A and Timmermans P B Comparison between the acute haemodynamic effects and brain penetration of atenolol and metoprolol J Cardiovasc Pharmacol 1 85 1979

Cruickshank J M Neil Dwyer G Cameron M M and McAinsh J Beta blockers and the central nervous system (Abstr) VIth Scientific Meeting of the International Society of Hypertension Gothenburg June 1979

Myers M G Lewis P J Reid J L and Dollery C T Brain concentration of propranolol in relation to hypertensive effect in the rabbit with observations of brain propranolol levels in man J Pharmacol Exp Ther 192 327 1975

Hemsworth B A and Street J A Accumulation of beta adrenoceptor antagonists in the lung (Abstr) VIIth International Congress of Pharmacology Paris July 1978

Simpson W T Nature and incidence of unwanted effects with atenolol Postgrad Med J 53 162 1977

Greenblatt D J and Koch Weser J Adverse reactions of propranolol in hospitalized medical patients a report from the Boston Collaborative Drug Surveillance Program Am Heart J 86 478 1973

Fleminger R Visual hallucinations and illusions with propranolol Br Med J 1 1182 1978

Fraser H S and Carr A C Propranolol psychosis Br J Psychiatry 129 508 1976

Mattiasson I and Henningsen N C Side effects during treatment with lipid soluble beta adrenergic blocking substances (Abstr) VIIIth World Congress of Cardiology Tokyo September 1978

Fleminger R Visual perceptual disorders and other central nervous system side effects a comparison between propranolol and atenolol (Abstr) VIth Scientific Meeting of the International Society of Hypertension Gothenburg June 1979

McAinsh J Clinical pharmacokinetics of atenolol Postgrad Med J 53 74 1977

Routledge P A and Shand D G Clinical pharmacokinetics of propranolol Clin Pharmacokinet 4 73 1979

Johnsson G and Regardh C G Clinical pharmacokinetics of beta adrenoceptor blockers Drugs 11 111 1976

Zech P Y Labeeuw M Pozet N Hadj Aissa A Sassard J and McAinsh J Response to atenolol in arterial hypertension in relation to renal function pharmacokinetics and renin activity Postgrad Med J 53 134 1977

Kirch W Schafer M Mutschler E and Kohler H Multiple oral doses of atenolol in patients with varying renal function and on dialysis R Soc Med International Congress and Symposium Series 19 Academic Press London and New York 1979

Warren D J Hood D and McAinsh J Atenolol in subjects with renal failure—a dose finding study R Soc Med International Congress and Symposium Series 19 Academic Press London and New York 1979

Lowenthal D T Briggs W A Gibson T P Nelson H and Cirksena W J Pharmacokinetics of oral propranolol in chronic renal disease Clin Pharmacol 16 761 1974

Hilton D D Pharmacokinetics of metoprolol in normotensive patients with end stage renal failure on regular dialysis Symposium Modern Aspects of Beta Blocker Therapy Dubrovnik Yugoslavia 5-8 April 1978

40 Thompson F D Joekes A M, and Foulkes, D M Pharmacodynamics of propranolol in renal failure Br Med J 2 434 1972

41 Davies D F and Shock N W Age changes in glomerular filtration rate effective renal plasma flow and tubular excretory capacity in adult males, J Clin Invest 29 496 1950

42 Thompson E N and Williams R Effect of age upon liver function with particular reference to bromsulphthalein excretion Gut 6 266 1965

43 Castleden C M, Kaye C M and Parsons R L The effect of age on plasma levels of propranolol and practolol in man Br J Clin Pharmacol. 2 303 1975

44 Castleden C M and George C F The effect of ageing on the hepatic clearance of propranolol Br J Clin Pharmacol 7 49 1979

45 Zacharias F J Long term clinical experience with atenolol R Soc Med International Congress and Symposium Series 19 Academic Press London and New York 1979

46 Greenblatt D J and Koch Weser J Adverse reactions to beta adrenergic blocking drugs, Drugs 7 118 1974

47 Robinson C Jackson G, Fisk C and Jewitt D Haemodynamic effects of atenolol in patients with coronary heart disease Br Heart J 40 22 1978

48 Tarazi R C and Dustan H P Beta adrenergic blockade in hypertension Am J Cardiol. 29 633 1972

49 Amery A De Plaen J F Lijnen P McAinsh, J and Reybrouck T Relationship between blood levels of atenolol and pharmacologic effect Clin Pharmacol Ther 21 691 1977

50 Lund-Johansen P Haemodynamic long term effects of a new beta adrenoceptor blocking drug atenolol (ICI 66 082) in essential hypertension Br J Clin Pharmacol 3 445 1976

51 Harry J D The demonstration of atenolol as a beta adrenergic blocking drug in man Postgrad. Med J 53 65 1977

52 Noer G H an Ekeli T Atenolol once daily in angina pectoris Curr Ther Res 24 17 1978

53 Kendall M J Brown D Grieve A and John V A Pharmacokinetic and pharmacodynamic studies on single oral doses of metoprolol in normal volunteers, Eur J Drug Metab Pharmacokinet 2 73 1977

54 Harry J D Marlow H F, and Shields, A G The effects of time on the activity of beta adrenoceptor blocking drugs, Br J Clin Pharmacol. 7 425 1979

55 Harry J D Cruickshank J M and Young J Once daily beta blockers and blood pressure response to exercise Lancet 2 250 1979

56 Robinson C, Birkhead J Crook B Jennings, K and Jewitt D Clinical electrophysiological effect of atenolol—a new cardioselective beta blocking agent Br Heart J 40 14 1978

57 Seipel L Breithardt G, and Dohrng H P Effects of atenolol and propranolol on sinus node and intracardiac conduction in man Z Cardiol 66 719 1977

58 Aberg H Plasma renin activity after the use of a new beta adrenergic blocking agent (ICI 66 082) Int J Clin Pharmacol. 9 98 1974

59 Wilcox R G Combination hypotensive therapy with atenolol bendrofluazide and hydrallazine Postgrad Med J 53 128 1977

weights (Abstr) VIII World Congres of Cardiology Tokyo September 1978
138 Tcherdakoff I H Collinrd M Berrard F Kreft C Dupay A and Bernaille J M Propranolol in hyper tension during pregnancy Br Med J 2 670 1978
139 Dubois D Tempervilk B Fetitcolas J Klipper A Beta blockers in at risk pregnancies, Nouv Presse Med 7 3760 1978
140 Lieberman B A Sturrat G M Cohen S L Beard R W and Pinker G D The possible adverse effect of propranolol on the fetus in pregnancies complicated by severe hypertension Br J Obstet Gynae ol 85 6 1978
141 Fiddler G I Propranolol and pregnancy Lancet 2 1974

Copyright Information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner s consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients This consent is given on the condition however that the copier pay the stated per copy fee through the Copyright Clearance Center Inc 21 Congress Street Salem Mass 01970 617 744 3350 for copying beyond that permitted by Sections 107 or 108 of the U S Copyright Law This consent does not extend to other kinds of copying such as copying for general distribution for advertising or promotional purposes for creating new collective works or for resale

adrenoceptor blocking agents and lipid metabolism Clin Sci Mol Med 55 323s, 1978

Waal Manning H J Atenolol and three non selective beta blockers in hypertension Clin Pharmacol Ther 25 8 1979

Comerford M B Selectivity of beta blockade in clinical medicine fact or fiction? Symposium Cardiovascular Disease 1978

Hansson L., Westerlund A Aberg H and Karlberg B E A comparison of the antihypertensive effect of atenolol (ICI 66 082) and propranolol Eur J Clin Pharmacol. 9 361 1976

Clausen N Damsgaard T and Mellemgaard K Antihypertensive effect of a non selective (propranolol) and cardioselective (metoprolol) beta adrenoceptor blocking agent at rest and during exercise Br J Clin Pharmacol 7 379 1979

Wright, A D Barber S G Kendall M J and Poole P H Beta adrenoceptor blocking drugs and blood sugar control in diabetes mellitus, Br Med J 1 159 1979

Astrom H and Vallin H Effect of a new beta adrenergic blocking agent ICI 66 082 on exercise haemodynamics and airways resistance in angina pectoris Br Heart J 36 1194 1974

Sangvik, K., Stokkeland M Landseth Ditlefsen E M and Nylberg G Circulation reaction at rest and during isometric and dynamic exercise in hypertensive patients *influence of different adrenergic beta adrenoceptor antagonists* Pharmatherapeutica 1 71 1976

Bateman, B N Dean C R Mucklow J C Bulpitt C J and Dollery C T Atenolol and chlorthalidone combination for hypertension Br J Clin Pharmacol 7 537 1979

Heidlreder E Pagel G., Röckel A and Heidland A. Beta adrenergic blockade in stress protection Limited effect of metoprolol in psychological stress reaction Eur J Clin Pharmacol 14 391 1978

Lloyd Mostyn R H and Oram S Modification by propranolol of cardiovascular effects of induced hypoglycaemia Lancet 1 1213 1975

Davidson N McD Corrall R J Shaw T R and French E B Observations in man of hypoglycaemia during selective and non selective beta blockade Scott Med J 22 69 1977

Lager I., Blohme G and Smith U Effect of cardioselective and non-selective beta blockade on the hypoglycaemic response in insulin-dependent diabetics Lancet 1 485 1979

Jackson G Harry J D Robinson C Kitson D and Jewitt D E Comparison of atenolol with propranolol in the treatment of angina pectoris with special reference to once daily administration of atenolol Br Heart J 40 998 1978

Silverton P N Stoker J B and Mellor J Atenolol and oxprenolol in angina pectoris, Postgrad Med J (In press)

Jackson, D A. Beta blockers and renal function Br Med J 1 1149 1979

a Hollenberg N K Adams D F McKinstry D N Williams G H Borucki L J and Sullivan J M Beta adrenoceptor blocking agents and the kidney Effect of nadolol and propranolol on the renal circulation Br J Clin Pharmacol 7 119S 1979

Day J L Simpson N Metcalf J and Page R L. Metabolic consequences of atenolol and propranolol in treatment of essential hypertension Br Med J 1 77 1979

116 Harms, H H Cardioselective beta-adrenoceptor blocking agents Human and animal studies in vitro and in vivo Amsterdam 1977 Enroprint BV Rijswijk pp 115-127

117 Deacon S P and Barnett D Comparison of atenolol and propranolol during insulin induced hypoglycaemia Br Med J 2 272, 1976

118 Galbo H., Holst, J J Christensen N C and Hilsted J Glucagon and plasma catecholamines during beta receptor blockade in exercising man J Appl Physiol. 46 805 1976

119 Deacon S P The effects of atenolol and propranolol upon lipolysis Br J Clin Pharmacol 5 193 1978

120 Waal Manning, H J Metabolic effect of beta adrenoreceptor blockers, Drugs 11 121 1976

121 Shand D G Propranolol N Engl J Med. 293 280 1975

122 Allison S P Chamberlain M J., Miller J E., Ferguson R Gillett A. P Bemand B V., and Saunders R A Effects of propranolol on blood sugar insulin and free fatty acids Diabetologia 5 339 1969

123 Skinner D J., and Misbin R. I Uses of propranolol, N Engl J Med 293 1205 1975

124 Raveno W S and Rosenbaum H Propranolol and hypoglycaemia, Lancet 1 920 1968

125 Kotler M N Berman L., and Rubenstein A H. Hypoglycaemia precipitated by propranolol Lancet 2 1389 1966

126 Feller J M Dangers of hypoglycaemia with use of propranolol Med J Aust 2 92 1973

127 McBride J T McBride M C and Viles, P H Hypoglycaemia associated with propranolol Pediatrics 51 1085 1973

128 Wray R and Sutcliffe S B J Propranolol induced hypoglycaemia and myocardial infarction Br Med J 2 592 1972.

129 Samu K., Cianciomi C H Rottembourg J., Bisseliches F and Jacobs C Severe hypoglycaemia due to beta blocking drugs in haemodialysis patients, Lancet 1 545 1976

130 Editorial Beta blockers for diabetics, Lancet 1 843 1977

131 Kurien V A., and Oliver M F A metabolic cause for arrhythmias during acute myocardial infarction Lancet 1 813 1970

132 Roland J M Wilcox R G Banks, D C Edwards, B Fentem P H., and Hampton J R. Effect of beta blockers on arrhythmias during six weeks after suspected myocardial infarction Br Med J 2 518 1979

133 Sirbulescu R Atenolol in the treatment of cardiac dysrhythmia Acta Therapeutica 3 109 1977

134 Barden T P and Stander R W Myometrial and cardiovascular effects on an adrenergic blocking drug in human pregnancy Am J Obstet Gynecol. 101 91 1968

135 Turner G M Oakley C M., and Dixon H G Management of pregnancy complicated by hypertrophic obstructive cardiomyopathy Br Med J 4 281 1968

136 Gregoric, G Majstorovic B Najdanovic B., and Popovic A. Clinical experience with propranolol in treatment of hypertension of pregnancy (Abstr) VIII World Congress of Cardiology Tokyo September 1978

137 Gyory A. Z., Gallery E D., and Hunyor S N Effect of treatment of maternal hypertension with oxprenolol and methyldopa on plasma volume placental and birth

Table I Distribution of patients and control groups

	No of subjects M/F	Age (years) range mean ± S D	No of subjects with idiopathic GIT bleeding (%) mean age ± S D	No of subjects with aortic stenosis (%) mean age ± S D
Subjects with AS (Case group A)	152 103/49	7 74 44 4 ± 16 3	4(2 6%) 57.5 ± 6 9	–
Subjects with MS (Control group A)	152 55/97	12 77 46 7 ± 15 1	0	–
Subjects with GIT bleeding (Case group B)	154 96/58	11 87 57 4 ± 15.2	–	9(5.8%) 60 9 ± 7.3
Routinely admitted patients without GIT bleeding (Control group B)	154 73/81	17 79 58 4 ± 14 3	–	3 (1.9%) 57 3 ± 27.5

M = male F = female GIT = gastrointestinal tract AS = aortic stenosis MS = mitral stenosis.

Table II Sources of bleeding and incidence of AS in patients with GIT bleeding (Case group B)

Source of bleeding	No of patients	Subjects with aortic stenosis
Duodenal ulcer	94	1
Diaphragmatic hernia	15	1
Diverticulosis of colon	5	0
GIT tumors	7	0
Esophageal varices	2	0
Drug induced	7	0
Idiopathic	24	7

Table III The age distribution according to sex in Case group A (aortic stenosis) and Case Group B (GI bleeding)

Age (year)	Case Group A F/M	Case Group B F/M
- 20	8/13	0/2
21 30	5/6	2/8
31-40	3/14	4/7
41 50	14/22	6/17
51 60	10/29	18/17
61 0	8/19	16/24
71	1/0	12/21
Totals	49 103	58/96

findings of A[illegible] typical findings at cardiac catheterization [illegible] AS proven at autopsy In the anemic patient [illegible] tolic murmur was regarded as significant [illegible] when it remained following blood transfusion [illegible] subsequent restoration of the hemoglobi[illegible] to normal values

Statistical analysis was done using the chi square test

Results

The distribution of the patients in the four groups is given in Table I and the sources of GIT bleeding in Case group B is given in Table II In Table III the age and sex distribution of the patients in Case groups A and B are summarized Seven patients (five males and two females) in Case group A (4 6%) had duodenal ulcer (three of them with melena) and four males (2 6%) had idiopathic GIT bleeding (in three of them repeated laparotomies did not disclose the source of bleeding) Their mean ages were significantly higher than that of the total group A ($p < 0.05$) (Table I) Only four patients (two males two females) of the control group A (2 6%) had duodenal ulcer and none had idiopathic GIT bleeding (Table I) No statistically significant difference was found between the patients with idiopathic GIT bleeding those with duodenal ulcer and the non bleeders regarding the cardiac output valve area use of anticoagulants or antiplatelet aggregating agents and incidence of diabetes mellitus and arterial hypertension Syphilis was not detected among the presently examined patients

Nine patients of Case group B (5 8%) had AS (in five of them the diagnosis was confirmed by autopsy in two by catheterization and in the other two it was based on clinical criteria [a to d]) Their mean age was significantly higher than that of the total Case group B ($p < 0.005$) (Table

stenosis associated with gastrointestinal ... A survey of 612 patients

uda Shoenfeld M D
hael Eldar M D
ı Bedazovsky M D
J Levy M D
Pinkhas M D
Tikva Israel

pite the sophisticated procedures used in the nosis of bleeding from the gastrointestinal (GIT) it is sometimes impossible to estab the source of the bleeding[1] An association een GIT bleeding of undetermined source aortic stenosis (AS) has been reported and hereby tried to assay the incidence of GIT ding of established and of undetermined on among patients with documented AS as well he incidence of AS in patients with GIT ding of undetermined origin

and methods

he patient material (data as to age and sex are n in Table I) consisted of

Case group A—152 patients with proven AS underwent cardiac surgery between the years 1978

Control group A—152 patients with proven ral stenosis (MS) who underwent cardiac sur y between the years 1971 1975

ll patients underwent preoperative cardiac in which cardiac output and aortic mitral valve areas were determined All the ients were examined diagnosed and operated in the same department In all of them the s was severe enough to warrant opera —ie in AS a gradient of at least 60 mm Hg een the aortic and the ventricular systolic pressures and in MS all patients were in function al Class of late II or III or suffered from arterial embolizations In 77 out of the 152 patients with AS an associated aortic insufficiency was found while in only 51 out of the 152 patients with MS was mitral insufficiency also found

GIT bleeding was defined as a drop of the hemoglobin to less than 11 5 g /dl in males and less than 10 5 g /dl in females associated with either three consequent positive guaiac stool examinations for the presence of occult blood or when melena occurred

All patients with GIT bleeding underwent a complete GIT x ray series including routine rec toscopies In 85% of the patients these examina tions were performed at least twice The bleeding was considered idiopathic when its source was not detected by the above mentioned examination Eight patients had gastroscopies (and in two of them-colonoscopies) celiac angiography as well as explorative laparotomy however even these procedures failed to establish the source of bleed ing In order to examine the incidence of AS among patients with idiopathic GIT bleeding two additional groups of patients were selected

1 Case group B—154 patients hospitalized for GIT bleeding between the years 1971 and 1975

2 Control group B—154 age matched patients selected from 154 consecutive admissions during 1974 who had no GIT bleeding (Table I)

The diagnosis of AS was established when at least four of the following criteria were present namely (1) systolic aortic ejection murmur radi ating to both carotid arteries (2) a low and slow radial pulse (3) a calcification of the aortic valve on chest x rays (4) typical echocardiographic

th D p rtme ts of I tern l Medi in D n l of Th ra ic d ho a c la Surgery the Sa kle S h l f Medi T l Avi B lin n Med cal C nt r P t h Tik I el

ed f r publ at n Dec 5 19 9
pted fo publ ation M rch 3 1980

it req est Y Shoenf ld M D D t tm t f I ternal Medi D B il son Med cal Ce t P t h Tik I r l

8 (/80/0801 9 + 04S00 40 0 1980 The C V Mosby Co

the AS does not justify this major operation Cattell (quoted in Ref 7) proposed a completely different approach namely a blind resection of the ascending colon This mode of treatment seems to be justified by the reports of GIT bleeding in patients with AS found to originate from the right colon[8, 9]

Summary

A retrospective study was done in order to examine the association between aortic stenosis (AS) and gastrointestinal tract (GIT) bleeding Four groups of patients included a group of 152 patients with AS a control group of 152 patients with MS, and another two groups of 154 patients each with and without GIT bleeding

GIT bleeding of known and of idiopathic sources was significantly more prevalent among patients with AS (three and four patients respectively) than among those with MS (none) Moreover AS was significantly more prevalent in association with idiopathic GIT bleeding (seven out of 24 29 1%) in comparison to its association with bleeding from a known source (two out of 130 1 5%) and its incidence in routinely admitted patients without GIT bleeding (three out of 154 1 9%)

This study supports the assumption that GIT bleeding may be associated with AS

REFERENCES

1 Rives J D and Emmett R O Melena A survey of two hundred and six cases, Am Surg 20 458 1954
2 Katz D Douvres P Weisberg H Charm R and Mckinnon W Sources of bleeding in upper gastrointestinal hemorrhage a reevaluation Am J Dig Dis 9 4 1961
3 Heyde F C Gastrointestinal bleeding in aortic stenosis (Letter) N Engl J Med 259 196 1958
4 Schwartz B M Additional note on bleeding in aortic stenosis, N Engl J Med 259 456 1958
5 Williams R C and Boston J R Aortic stenosis and unexplained gastrointestinal bleeding Arch Intern Med 108 103 1961
6 Cody M C O Donovan P B and Hughes R W Idiopathic gastrointestinal bleeding and aortic stenosis Am J Dig Dis 19 393 1974
7 McNamara J J and Austen W G Gastrointestinal bleeding in patients with acquired valvular heart disease Arch Surg 97 538 1968
8 Catelman B and McNeely B V Case records of the Massachusetts General Hospital N Engl J Med 273 1096 1965
9 Galloway S J Casarella W J and Shimkin P M Vascular malformation of the right colon as a cause of bleeding in patients with aortic stenosis Radiology 113 11 1974
10 Boss E C and Rosenbaum J M Bleeding from the right colon associated with aortic stenosis Am J Dig Dis 16 269 1971
11 Livne P Eldar M Shoenfeld Y Dintsman M and Pinkhas J Recurrent gastrointestinal bleeding associated with aortic stenosis Harefuah 95 59 19 8

IMPORTANT
INFORMATION FOR AUTHORS

Effective June 1 1980, all manuscripts for the AMERICAN HEART JOURNAL should be sent to

Dean T Mason M D
Section of Cardiovascular Medicine
University of California
School of Medicine
Davis California 95616

IV The age sex and type of valvular defect in 4 groups of patients with aortic stenosis and athic GI bleeding (AS + IGIB) IGIB + AS AS + duodenal ulcer (DU) and mitral stenosis + DU

bject No	AS + IGIB (4/152)		IGIB + AS (7/154)		AS + DU (7/152)			MS + DU (4/152)		
	Age	Sex	Age	Sex	Age	Sex	T	Age	Sex	T
1	64	M	76	M	51	M	C	71	M	R
2	48	M	70	M	54	M	C	50	F	R
3	61	M	63	M	25	M	R	60	F	R
4	57	M	72	F	66	M	C	69	M	U
5			60	F	67	M	C			
6			66	F	65	F	C			
7			82	F	41	F	R			

ype of valvular defect R = rheumatic C = calcified U = unclassified

en of them had AS—i e 29 1% of the its with idiopathic GIT bleeding (seven out 4) in contrast to only 1 5% (two out of 130) AS confirmed by autopsy among the with an established source of GIT bleed p < 0 001) (Table II) Only three cases of AS y diagnosed (1 9%) were found in the trol group B (p < 0 05)

he age sex and type of valvular defect in four ips of patients with GIT bleeding and valvu efect are summarized in Table IV

on

presently reported data reaffirm the asso between AS and idiopathic GIT bleeding latter being significantly more prevalent ong patients with AS compared to the control with MS In addition the incidence of AS our patients with GIT bleeding (Case p B) was significantly higher than among ely admitted patients without GIT bleed Control group B) (nine versus three Table I) over almost one third of the idiopathic GIT rs had associated AS (Table II) an inci ice comparable with the one reported by Wil and Boston [5]

n the present report the mean age of the ients having AS associated with GIT bleeding significantly higher than that observed in ir respective groups (Table I) Assuming that atherosclerotic process progresses with ancing years it might be possible that involve of both the aortic valve and the GIT vessels atherosclerotic lesions in older patients could responsible for this peculiar association other possible explanation for the GIT bleeding might be an ischemic damage to the intestinal vessel walls due to a decreased cardiac output in patients with AS [4] This possibility could not be supported by our data i e there was a lack of significant differences in cardiac output between GIT bleeders with AS or with MS The high incidence of syphilis found by Williams and Boston[5] among their patients with AS and idiopathic GIT bleeding was not noted among the presently examined patients Duodenal ulcer was found in 4 6% of our patients with AS (seven out of 152) a rate significantly higher than in the control group with MS (2 6%) McNamara and Austen[7] diagnosed duodenal ulcer in 18 of their 26 patients with AS We are unable to forward a reasonable explanation for this interesting association Many patients with AS are treated postoperatively with anticoagulants or antiplatelet aggregation agents Since duodenal ulcers have a propensity to bleed especially when the patient is on anticoagulants a search for duodenal ulcer might be recommended in every patient with AS facing operation

In a considerable percentage of patients with AS and GIT bleeding the GIT x rays series endoscopy angiography and explorative laparotomy failed to reveal the source of the bleeding [5, 7, 9, 10] Some of these quite aggressive diagnostic procedures bear considerable morbidity and mortality and may be dangerous especially in patients with valvular diseases McNamara and Austen[7] reported that recurrent episodes of GIT bleeding ceased following aortic valve replacement However these patients are frequently afflicted also by other valvular defects are of an advanced age and in many of them the severity of

Table I Effects of a moderate acute intravenous sodium load on the excretion of various ions in healthy subjects and in hypertensive patients

	C × 100/GFR (%)		C × 100/GFR (%)		C_c × 100/GFR (%)		C_M × 100/GFR (%)		C_P × 100/GFR (%)		C × 100/GFR (%)	
	N	H	N	H	N	H	N	H	N	H	N	H
Baseline	1 75 ± 0 68	1 60 ± 0 36	15 85 ± 3.50	19 24 ±* 1 90	4 20 ± 0 64	3 53 ± 0 52	5 10 ± 0 54	4 14 ± 0 86	10 72 ± 1 49	8 54 ± 1 48	2.73 ± 0 80	2.30 ± 0 41
During NaCl loading	4 56 ± 2 20	5 64 ± 1 08	14 09 ± 1 73	23 19 ± 2 26	6 41 ± 1.87	6 98 ± 1 19	7 26 ± 2 04	6 98 ± 1 36	21 70 ± 3.21	18 10 ± 2 18	5 68 ± 1 44	8 26 ± 1.59
After loading	4 78 ± 0 79	5 65 ± 0 73	23 79 ± 1 64	34 48 ± 2 57	4 95 ± 0 94	4 85 ± 0 85	4 51 ± 0 47	3 97 ± 0 70	31 03 ± 3 18	29 07 ± 2.99	6 38 ± 1 13	9 06 ± 1 13
Maximal change	6.29 ± 2 12	7 61 ± 1.36	14 10 ± 3 97	20 76 ±* 3 03	4 04 ± 1 91	6 67 ± 1.33	3 64 ± 2 40	5 76 ± 1 39	23 65 ± 4 00	29 08 ± 3 48	5.57 ± 0 90	14 01 ± 2.67
p <	0 05	0 001	0 05	0 001	NS	0 005	NS	0 01	0 01	0 001	0 05	0 01

N = healthy subjects (n = 4) H = hypertensive patients (n = 9) = not significant = p < 0 05 (hypertensive vs normal)
Moderate" NaCl load = intravenous infusion of 2 92% NaCl during 60 minutes During NaCl loading = mean of periods 2 to 6.
After loading = mean of periods 7 to 10 Maximal change = mean of individual maximum (in a single period from 3 to 10) *minus baseline*
Data are presented as mean ± SEM

patients with abnormal (low or high) plasma renin activity values[17] were excluded from the study A part of the study (Protocol I) was carried out in the University Hospital Utrecht The Netherlands and the other part (Protocols II and III) in the János Hospital Budapest Hungary The investigations were carried out according to the Declaration of Helsinki The nature of the investigation was fully explained to each person and written consent was obtained from them All antihypertensive treatments were discontinued 1 month before the study All participants (except three hypertensive patients) were placed on a diet containing 200 mEq Na per day for 4 to 7 days before the study In three members of the hyper tensive group H (see below) the daily Na intake was 150 mEq

Protocols

Protocol I Moderate NaCl loading in four healthy subjects (group N_1) and in nine hyperten sive patients (group H) Two days before the study 40 μg DDAVP (Minirin Ferring AB Mal mo Sweden) was given intranasally (20 μg into each nostril) three times a day On the day of the study of 7 A M and 11 A M 40-40 μg DDAVP were given intranasally The study began after an overnight fast and water deprivation at 9 A M After two 30 minute control clearance periods (baseline study) 1 liter 2 92% NaCl solution (500 mEq Na) was infused during 60 minutes During this period and in the next hour altogeth er six 20 minute clearance periods were run The study was concluded by two 30 minute periods Altogether 10 periods were done during 4 hours

Protocol II/a High NaCl loading by rapid *infusion in four healthy subjects* (group N_2) The procedure was the same as in Protocol I except 2 liters 2 92% NaCl (1 000 mEq Na) were infused during 60 minutes an intravenous dose of 4 μg DDAVP was given at 9 A M in addition to the two intranasal doses given at 7 A M and 11 A M

Protocol II/b High NaCl loading by rapid infusion in three hypertensive patients (group H_2) The procedure was the same as in Protocol I except 1½ liters 2 92% NaCl were infused during 80 minutes

Protocol III High NaCl loading by slow infusion in seven healthy subjects (group N_3) Prepatatory DDAVP treatment was not given but during the whole experiment 500 mU lysine-vasopression per hour were infused intravenously No baseline periods were run One liter 2 5% NaCl was infused *intravenously* during the first two hours and 500 ml 5% NaCl was infused during the second two hours Altogether 854 mEq Na were given During the last hour one 60 minute clear ance period was performed

Urine was collected by an indwelling catheter Blood samples were taken through an indwelling venous catheter (Butterfly Abbott) in periods 1,2 5 7 and 9 of Protocols I II/a and II/b and at midpoint of the clearance period *of Protocol* III

:enal response to graded ıntravenous ypertonıc NaCl ınfusıon ın healthy and ypertensıve subjects dose-related ımpaırment ı dıstal NaCl reabsorptıon*

ınos P Radó M D
va Juhos M D
vert J Dorhout Mees M D
ıdapest Hungary and Utrecht The Netherlands

nhanced sodıum excretıon after a salt load has :en descrıbed as exaggerated natrıuresıs (EN) patıents wıth varıous forms of hypertensıon [1] s mechanısms and the renal sıte of ımpaıred dıum reabsorptıon have been extensıvely ınves gated but are ıncreasıngly controversıal ın the cent lıterature A prımary tubular defect or an ınormal response to volume expansıon were ınsıdered as possıbly responsıble for the phe ımenon[9 11] and a predomınant role was claımed r both the proxımal tubules[5 8] and the dıstal ephron[8 11] The abnormal renal handlıng of sodı n prevıously was thought to be characterıstıc to l patıents wıth essentıal hypertensıon but very cently ıt was postulated as a feature of renın ıppressıon[12 14] Our prelımınary studıes sug ısted that depressıon of free water reabsorptıon ($T^c_{H_2O}$) was a more sensıtıve ındıcator of the altered nal response to acute NaCl loadıng than EN self becomıng more pronounced wıth ıncreasıng ıe load Furthermore a sımılar tendency was und also ın the healthy persons when very hıgh aCl loads were used Therefore the present ork was desıgned to compare the renal responses healthy subjects and normal renın essentıal hypertensıve patıents to graded acute ıntrave nous hypertonıc NaCl loadıng wıth specıal refer ence to changes ın the normal relatıonshıp between solute excretıon (osmolal clearance Cosm) and $T^c_{H_2O}$ From such a comparıson we expected to exclude an ıntrınsıc tubular abnor malıty and to demonstrate that EN ıs an acute renal response abnormally reset to a lower level ın the hypertensıve patıents

om th Departm nt of Medıcıne Janos Hosp tal, Budapest, Hunga and th Departm nt of Nephrology Unıversıty Hosp tal Utrecht, ıe Netherlands

ceıved for publıcatıon Oct 30 19 8

c pted for publıcat on March 26 19 9

prınt requests Dr János P Radó Dept. of Medıcın Janos sp tal, XII D osarok u 1 H 1125 Bud pest Hungary

hıs study was supported by the Dutch Kıdn y Foundatıon

Materıals and methods

Partıcıpants Studıes were performed on 12 patıents wıth uncomplıcated essentıal hyperten sıon (average age 34 3 ± 2 9 (SEM) years) and on 15 healthy volunteers (average age 23 5 ± 1 9 years) In the Protocol I and II studıes (see below) sıx male and two female healthy subjects and 10 male and two female hypertensıve patıents par tıcıpated Protocol III was performed on four male and three female healthy persons In the hypertensıve groups the elevatıon of blood pres sure was from mıld to moderate and all patıents were free from any demonstrable cardıovascular renal or endocrınologıcal consequences of long standıng hypertensıon Normal renal functıon was assessed by urıne analysıs creatınıne clear ance and DDAVP* concentratıon test [5] Reno vascular hypertensıon was ruled out by normal radıorenogram ıntravenous pyelogram and ın certaın cases by renal arterıogram Other forms of secondary hypertensıon were excluded by appro prıate tests ıncludıng renal bıopsy Hypertensıve

1 Desamıno-8-D Argınıne Vasopressın.

)02 8703/80/080183 + 08$00 80/0 © 1980 The C V Mosby Co

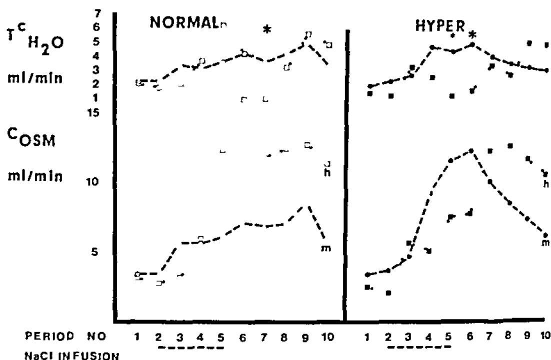


Fig 2 Time course of changes in solute excretion *(Cosm)* and free water reabsorption (T_{H_2O}) during and after acute intravenous NaCl loading in normal subjects and in hypertensive patients. Note the transitory decrease in $T^c_{H_2O}$ after a high NaCl load *(h)* apparently not related to changes in Cosm in both groups. Moderate" NaCl load *(m)* induced expected changes

Table II Effects of graded acute intravenous sodium loading on the excretion of various ions in healthy subjects

	C × 100/GFR (%)		C_K × 100/GFR (%)		C × 100/GFR (%)		C_M × 100/GFR (%)		C_i × 100/GFR (%)		C_P × 100/GFR (%)	
	N	N	N	N	N	N	N	N	N	N	N	N
Baseline	1 75 ± 0 68	1 03 ± 0 18	15 85 ± 3 50	19 05 ± 4.21	4.20 ± 0 64	3.55 ± 0 79	5 10 ± 0 54	4.56 ± 0.26	13 32 ± 2 73	10.23 ± 0 64	10 72 ± 1 49	6.98 ± 0 59
During NaCl loading	4 .6 ± 2 20	6 08 ± 1 04	14 09 ± 1 73	20 6 ± 2 66	6 41 ± 1 87	9.22 ± 2 30	7.26 ± 2 04	11 89 ± 0 89	11.23 ± 1.56	11 08 ± 1.13	21 70 ± 2.21	18 65 ± 3.95
After loading	4 78 ± 0 79	10 42 ± 1 35	23 79 ± 1 64	48 66 ± 2.58	4.95 ± 0.94	10 42 ± 1.53	4.51 ± 0 47	9 03 ± 0 68	11 17 ± 1 80	14..8 ± 1 69	31 03 ± 3 18	36 17 ± 6 49
Maximal change	6.29 ± 2.12	13.81 ± 2.85	14 10 ± 3.97	39 84 ± 4 47	4 04 ± 1.91	15 81 ± 2.99	3 64 ± 2 40	12.81 ± 1.53	–3 30 ± 1.33	6 36 ± 1 14	23 65 ± 4 00	25 47 ± 11 47
p <	0 05	0 05	0 01	0 001	NS	0 005	NS	0 001	0 05	0 02	0 001	0 05

N = four healthy subjects 1 liter 2.9?% NaCl during 1 hour N = four healthy subjects 2 liters 2.92% NaCl during 1 hour = n t significant = p < 0 05 = p < 0 01 = p < 0 001

There was a parallel rise in both parameters up to period 9 during and after NaCl infusion The relationship is expressed by the formula y = 0.50 × + 0 52 (r = 0 95 p < 0 001) (Fig 1) The slope of this line was not significantly different from that of the baseline relationship The relationship between Cosm and $T^c_{H_2O}$ remained constant when Cosm was increased either by prolonged high Na intake or by acute intravenous NaCl loading

Hypertensive patients (group H) The relationship between Cosm and T_{H_2}, is expressed by the formula y = 0 36 × + 0 79 (r = 0 82 p < 0 001) The slope of this line was significantly different from that of the baseline relationship (p < 0 05 Fig 1) Fractional Cl and K excretion increased to

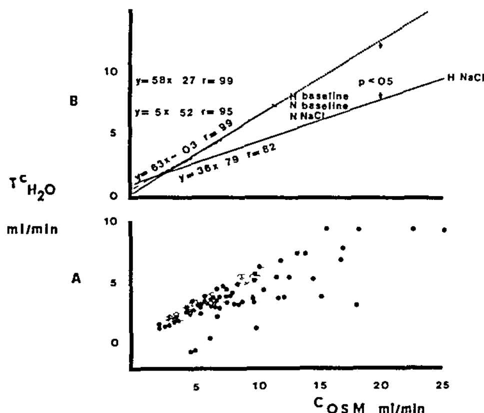


Fig 1 Relationship between Cosm and $T^c_{H_2O}$ under the influence of a moderate" intravenous NaCl load in healthy *(circles N)* and in hypertensive *(black dots H)* subjects *A* All T^c values obtained during and after intravenous NaCl loading were plotted against Cosm. *B* Regression lines of data of baseline and NaCl studies. Note the significant difference between the slopes in the hypertensi e group *(solid line baseline extrapolated)* vs no difference in the healthy group *(dashed line)* *Asterisk* = $p < 0.05$

rine and blood samples were analyzed for creat ine sodium potassium (in all groups) calcium agnesium phosphate (in all but group N_1) and r uric acid (only in groups N and N_2) by ocedures applied to the Technicon Autoanalyz Chloride was measured by a chloridometer All n clearances were expressed as a percentage of FR (creatinine clearance) When calculating Ca nd Mg clearances it was assumed[16] that 60% of e total plasma Ca concentration and 70% of the tal Mg concentration underwent ultrafiltration the glomerulus Osmolality was determined by n Advanced Osmometer Cosm and T_{H_2O} were lculated according to standard formulas In rder to save space in the Tables contracted data f periods 1 and 2 (baseline) 3 to 6 (during aCl loading) and 7 to 10 (after loading) are cluded For unity period 6 was included in the during NaCl loading contracted data of Proto ols I and II/a Correlation coefficients and gression lines were computed by the method of ast squares Statistical significance was deter mined by the paired t test except when different groups were compared then the unpaired t test was used Data are presented as mean ± SEM

Results

Baseline relationship between Cosm and $T^c_{H_2O}$ A normal relationship between Cosm and $T^c_{H_2O}$ was established during high NaCl intake by including all baseline values of the healthy sub jects (groups N_1 and N) and hypertensive patients (groups H_1 and H_2) The relationship is expressed by the formula $y = 0.58 \times + 0.27$ ($r = 0.99$ $p < 0.001$) in the healthy subjects and by $y = 0.63 \times - 0.03$ ($r = 0.99$ $p < 0.001$) in the hypertensive patients No statis tical difference was found between the slopes (Fig 1)

Effect of a moderate intravenous NaCl load on the baseline relationship between Cosm and T_{H_2O}

Healthy subjects (group N_1) The time course of changes in Cosm and T_{H_2O} can be seen in Fig 2

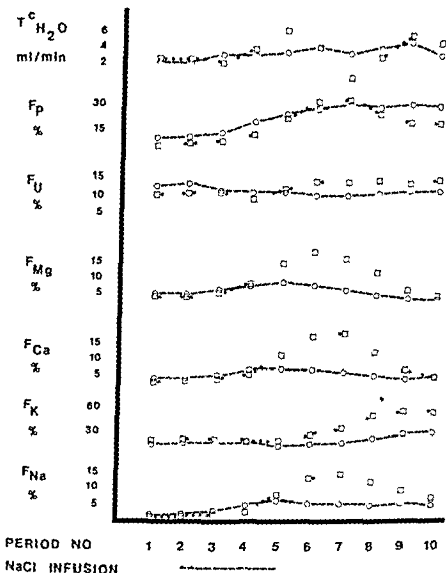


Fig 4 Time course of changes in *fractional* excretion of Na K Ca Mg uric acid *(U)* and phosphate *(P)* as well as in T^c during and after moderate NaCl loading *(circles)* and high NaCl loading *(squares)* $p < 0.05$ $p < 0.01$ $p < 0.005$ $p < 0.001$

NaCl reabsorption in Henle s loop Our most striking finding was the disruption of the normal correlation between Cosm and T_{H_2O} with some times positive free water clearance values when healthy subjects were infused with high intrave nous NaCl loads Our results are in agreement with those obtained in other studies of the hydrated dog and of human subjects [6] suggesting that volume expansion inhibits fractional NaCl reabsorption in the distal nephron in a dose related fashion Depression of the fractional NaCl reabsorption in the distal nephron obviously played a definitive role in the exaggeration of natriuresis when high NaCl loads were given to healthy subjects The peak fractional Na Ca and Mg excretions were simultaneous with the decrease in T_{H_2O} (Fig 4) also supporting the hypothesis that the reabsorption of interrelated ions [4] was inhibited in the distal nephron If fractional phosphate excretion is (within limitations) an acceptable proximal marker [9] then the lack of difference in phosphaturia between the moderate and high NaCl groups seems to support the distal interpretation (Table II)

An alternative explanation for the observed depression of $T^c_{H_2O}$ would be insufficient osmotic equilibration in the collecting tubules as a result of excessive osmotic diuresis or/and submaximal ADH effect This however probably was not the case because osmotic diuresis (Cosm) was not

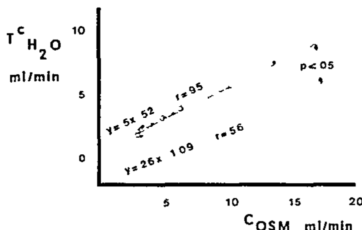


Fig 3 Relationship between Cosm and $T^c_{H_2O}$ in healthy subjects under the influence of "moderate" NaCl loading *(group N circles)* and high NaCl loading *(group N black stars)*

significantly higher level in this group than in oup N_1 but there was no significant difference Na Ca Mg and P excretion between the oups (Table I)

Effect of high intravenous NaCl loads on the ationship between Cosm and T_{H_2O} established ring moderate NaCl loading

Healthy subjects (group N_2, Protocol II/a) The ationship during high NaCl loading is pressed by the formula $y = 0\,26 \times + 1\,09$ $= 0\,56$ $p < 0\,001$) The slope of this line was nificantly different from that of moderate ading ($p < 0\,05$) The correlation between sm and $T^c_{H_2O}$ became much less close after a gh NaCl load than after a moderate load (Figs and 3) There was a significant difference $< 0\,001$) between the mean maximum and nimum $T^c_{H_2O}$ values (6 74 ± 0 48 ml /minute vs 2 ± 0 61 mL/minute) obtained during high aCl loading but without a significant difference tween the corresponding mean Cosm values 17 ± 1 24 ml /minute vs 11 92 ± 1 57 ml / nute) suggesting that the rise of Cosm per se as not responsible for the dramatic decrease in o (Fig 2) The rises in fractional Na K Ca Mg d Cl excretions were significantly higher after gh NaCl loading than after moderate NaCl ading (Table II Fig 4) but there was no nificant difference in P excretions It is inter ting that fractional uric acid excretion slightly creased after moderate NaCl loading but sig ficantly increased in response to a high NaCl ad

It should be noted that during administration a relatively high dose of NaCl by *slow* intravenous infusion *(group N_3 Protocol III)* the correlation between changes of Cosm and T_{H_2O} remained excellent $r = 0\,99$, $p < 0\,001$)

Hypertensive patients (group H_2, Protocol II/ b) The relationship between Cosm and T_{H_2O} (ex pressed by the formula $y = 0.27 \times +0\,59$) was less close after high loading ($r = 0\,49$ $p < 0\,05$) than after a moderate load in group H_1 ($r = 0.82$ $p < 0\,001$) There was a significant difference ($p < 0\,001$) between the mean maximum and minimum $T^c_{H_2O}$ values (5 87 ± 0 43 ml /minute vs 0 86 ± 0 59 ml /minute) but no significant difference was found in the corresponding mean Cosm values (11 09 ± 1 42 ml /minute vs 7 92 ± 1 81 ml /minute)

Discussion

This study clearly shows that acute NaCl loading may depress T_{H_2O} not only in hypertensive patients[9, 10] but also in healthy subjects (Figs 1 to 3) In earlier studies carried out in dehydrated healthy subjects this has not been reported because during intravenous administration of hypertonic NaCl solutions there was no evidence for an upper limit of T_{H_2O} as the increasing delivery from the proximal nephron enhanced NaCl transport out of the ascending limb of Henle s loop[8] However in the previous studies only moderate NaCl doses were used[13] and the present results show that depression of $T^c_{H_2O}$ occurred apparently as a dose related consequence of acute NaCl loading The augmentation of $T^c_{H_2O}$ at any rate of distal delivery of NaCl was significantly less during high NaCl loading than after moderate NaCl loading suggesting impaired

tional reabsorption of urate and other ions in normal and hypertensive man Circulation 41 97 1970
17 Haber E Koerner T Page L. B Kliman B., and Purnode A. Application of a radioimmunoassay for angiotensin I to the physiologic measurements of plasma renin activity in normal human subjects J Clin Endocrinol Metab 29 1349 1969
18 Goldberg M McCurdy D K and Ramirez M A Differences between saline and mannitol diuresis in hydropenic man, J Clin Invest 44 182, 1965
19 Massry S G., Friedler R M., and Coburn J W Excretion of phosphate and calcium Arch. Intern Med 131 828 1973
20 Alexander E A., Doner D W., Auld R. B and Levinsky N G Tubular reabsorption of sodium during acute and chronic volume expansion in man J Clin Invest 51 2370 1972
21 Danovitch G M and Bricker N S Influence of volume expansion on NaCl reabsorption in the diluting segments of the nephron A study using clearance methods, Kidney Int 10 229 1976
22. Ish-Shalom N., Rapoport, J Chaimovitz C and Better O S The effect of acute extracellular volume expansion on sodium chloride reabsorption in the diluting segment in man Clin Sci. Mol. Med. 54 333 1978

IMPORTANT
INFORMATION FOR AUTHORS

Effective June 1 1980 all manuscripts for the AMERICAN HEART JOURNAL should be sent to

Dean T Mason M D
Section of Cardiovascular Medicine
University of California
School of Medicine
Davis California 95616

her when the lowest $T^c_{H_2O}$ values were measured in in the presence of the maximal $T^c_{H_2O}$ values d special care was taken to provide the subjects h supramaximal amounts of DDAVP [15] before d during the experiment The persistence of the se correlation between Cosm and $T^c_{H_2O}$ in group (given not much less NaCl but in slow intra ous infusion) underlined the significance of speed of acute loading in disruption of the rmal relationship

Our study confirmed that impaired NaCl trans rt in Henle s loop is a normal renal response to ertain degree of volume expansion In hyper nsive persons this response is found even after atively small NaCl loadings which do not cause y distortion in the normal relationship between sm and $T^c_{H_2O}$ in the healthy subject Therefore N in the hypertensives seems not to be due to an rinsic renal tubular defect but is probably the nsequence of a basically normal renal response et to a lower level

It was concluded that (1) impaired distal NaCl absorption may also occur in response to acute Cl loadings in the dehydrated healthy subject d (2) EN is a normal renal response abnormally et to a lower level in the hypertensive tient

mmary

The effects of graded acute intravenous hyper nic NaCl loads on the baseline relationship tween osmolal clearance and free water reab ption established during high NaCl dietary ake and on the fractional excretion of various s were investigated in 15 healthy subjects and 12 normal renin essential hypertensive tients No significant influence on the baseline ationship could be demonstrated after a *mod ate* NaCl load in the healthy subjects while e water reabsorption was depressed by the me intervention in the hypertensive patients gh NaCl loads induced depression of free water absorption in a dose related fashion in both ups No difference was found in phosphaturia tween the groups after the same NaCl load as ll as in the healthy persons after different NaCl ds supporting the contention that the served differences in free water reabsorption re not due to changes in the proximal nephron was concluded that (1) impaired NaCl reab rption in Henle s loop (depression of free water absorption) may also occur in response to acute NaCl loadings in healthy subjects and (2) exag gerated natriuresis is the consequence of a normal renal response (impaired NaCl transport in Henle s loop) to a certain degree of volume expansion reset abnormally to a lower level in hypertensive patients

REFERENCES

1 Farnsworth E B Renal reabsorption of chloride and phosphate in normal subjects and in patients with essential hypertension J Clin Invest 25 897 1946

2 Cottier P T, Weller J M and Hoobler S W Effect of an intravenous sodium chloride load on renal hemodynamics and electrolyte excretion in essential hypertension Circulation 17 750 1958.

3 Rovner D R Conn J W Knopf R F Cohen E L, and Hsuch M T Y Nature of renal escape from the sodium retaining effect of aldosterone in primary aldosteronism and normal subjects J Clin Endocrinol. 25 53 1965

4 Rado J P Tako J and Szabo T Salt loading in renal aldosteronism before and after nephrectomy Arch Surg 98 357 1969

5 Baldwin D S Biggs A W Goldring W Hulet W H and Chasis H Exaggerated natriuresis in essential hypertension Am J Med 24 893 1958

6 Dorhout Mees E J and de Graaf H Free water clearance in patients with essential hypertension, Clin Sci. Mol Med 45 469 1973

7 Chaimovitz C, Spierer A., Leibowitz H Tuma S and Better O S Exaggerated phosphaturic response to volume expansion in patients with essential hypertension Clin Sci Mol. Med 49 ?07 1975

8 Raeder M Omvik, P and Kiil F Effect of acute hypertension on the natriuretic response to saline loading Am J Physiol 226 989 1974

9 Buckalew V M Puschett, J B., Kintzel, J E and Goldberg M Mechanism of exaggerated natriuresis in hypertensive man Impaired sodium transport in the loop of Henle J Clin Invest 48 1007 1969

10 Rado J P Szende, L., Borbely L. Banos Cs Tako J and Fischer J Different effects of frusemide administered during hypertonic saline infusion in healthy subjects and hypertensive patients, Clin Sci 39 833 1970

11 Viskoper R J Ben Ishay D and Aviram A Lack of exaggerated phosphaturia in essential hypertension Nephron 13 390 1974

12 Krakoff L R Goodwin F J Baer L. Torres M and Laragh J H The role of renin in the exaggerated natriuresis in hypertension Circulation 42 335 1970

13 Schalekamp M A. D H Krauss X H., Schalekamp-Kuyken M P A Kolsters G and Birkenhager W H Studies on the mechanism of hypernatriuresis in essential hypertension in relation to measurements of plasma renin concentration body fluid compartments and renal function Clin Sci. 41 219 1971

14 Luft F C Grim C E Willis L R Higgins J T., and Weinberger M H Natriuretic response to saline infusion in normotensive and hypertensive man. The role of renin suppression in exaggerated natriuresis, Circulation 55 779 1977

15 Rado J P 1 Desamino-8-D Arginine Vasopressin (DDAVP) cocentration test Am J Med. Sci 275 43 1978

16 Cannon P J Svahn D S and Demartini, F E The influence of hypertonic saline infusions upon the frac

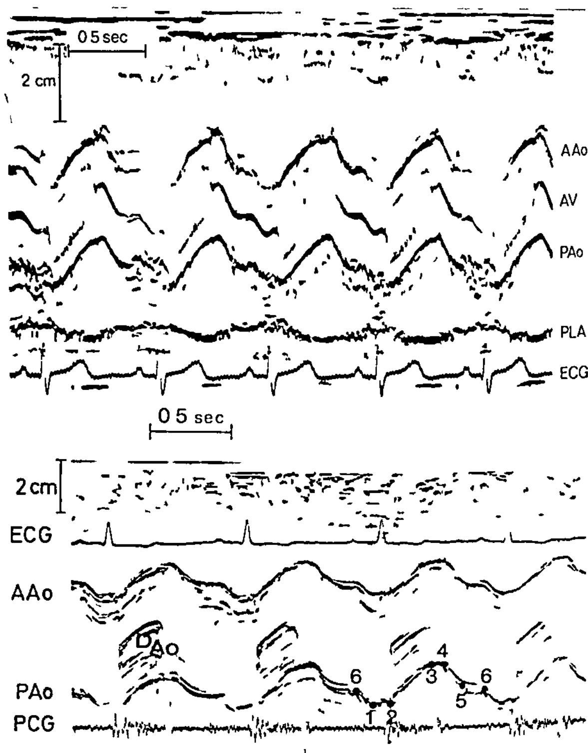


Fig 1 *a (upp[illegible] [illegible]nel)* Echogram of the aortic root of a healthy ten year old child Note the typical box like systolic conf[illegible]ration of the aortic cusps In diastole the cusps produce a midline echo configuration *(A V)* Closure of the aortic [illegible] has already taken place before the dorsally directed motion of the aortic root begins Note the synchronou[illegible] d[illegible] directed motion of the posterior left atrial wall *(PLA)* accompanying ventrally directed motion of the [illegible] and the resultant increase in the diameter of the left atrium *b (lower panel)* Echograms of the aortic ro[illegible] of a 26 year old man with a tilting Bjork Shiley valve prosthesis 1 to 6 are characteristic points in the cyclical a[illegible] r[illegible]ot configuration (for detail see text) *ECG*-electrocardiograms *AAo* and *PAo* = anterior and posterior [illegible] f the aortic root D_A = tilting disc of the Bjork Shiley valve in the opened position *PCG* = phonoca[illegible]gr[illegible]ms taken right parasternally in the second intercostal space

Echocardiographic pattern of motion of the aortic root as a correlate of left atrial volume changes*

G Biamino
H J Wessel
W Schlag
R Schroeder
Berlin W Germany

The pattern of motion of the aortic root is characterized by parallel movement of its anterior and posterior walls and is usually simple to record echocardiographically The distance between the two walls as a correlate of the diameter of this vascular structure -4 and evaluations of the aortic leaflet motion between the two dominant echos- have been the subject of several investigations Recently attempts have been made to correlate the typical systolic motion of the aortic root in the direction of the anterior wall of the thorax with the stroke volume of the left ventricle

When recording the echoes of normal aortic leaflets and particularly during postoperative studies of Bjork Shiley aortic valve prostheses it was noted that the systolic motion of the aortic root towards the anterior thorax wall uniformly continues beyond closure of the valve This finding indicates that a direct correlation between stroke volume of the left ventricle and systolic aortic root motion is doubtful

In this study we have therefore attempted to correlate the motion of the aortic root with further echocardiographically detectable structures and with the ECG the PCG the carotid pulse curve or the apexcardiogram as well The results indicate that the echocardiographically detectable motion of the aortic root is not caused by the volume ejected into the aorta during systole but is an index of changes in volume of the left atrium *

Similar conclusions have been reported by Strunk and associates in recent studies comparing hemodynamic and cineangiographic findings with the simultaneously recorded echocardiographic pattern of the posterior aortic wall

Material and method

Forty-eight male and 34 female patients aged between 10 and 68 years (average age 54 years) were studied In 32 cases the studies were performed during routine examinations after implantation of aortic and/or mitral valve prostheses (Bjork Shiley tilting disc valve) There were no clinical or echocardiographic signs of malfunction of the prostheses The prostheses in the aortic position were implanted with a standardized operative procedure in such a way that the asymmetric strut was positioned left anteriorly between the two coronary ostia In consequence the disc opening movement turned in a left anterior direction toward the ultrasonic beam In the mitral position the strut of the prostheses was placed so that the protodiastolic major disc pivoted toward the aortic outflow tract in the direction of the septum and, thus also in a ventral direction toward the transducer * In the remaining 50 cases there was no sign of an aortic or mitral defect

From the Department of Cardiology Medical Clinic of the Free University Klinikum Steglitz, Berlin, W Germany

Received for publication Dec 6. 1978

Accepted for publication March 1 1979

Reprint requests. Dr G Biamino Abteilung fur Kardiopulmonologie Klinikum Steglitz der FU Berlin, Hindenburgdamm 30 1000 Berlin 45 W Germany

*The results of this study were presented in part at the Seventh European Congress of Cardiology in Amsterdam The Netherlands in June, 1976, and at the Meeting of the Deutsche Gesellschaft fur Kreislaufforschung in Vienna, in October 1976.

0002-8703 80 080191 + 10$01.00 0 1980 The C V Mosby Co

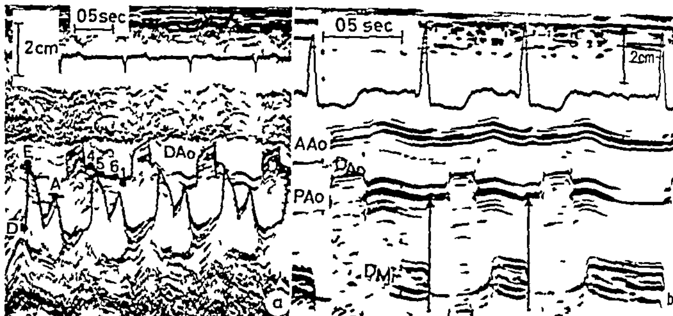


Fig 3 *a* On simultaneous registration of the posterior walls of the aortic root and of the tilting disc of the valve prosthesis (D_A) and of the anterior mitral leaflet *(D E A)* it can be clearly seen (1) that Point 4 in aortic root motion is concomitant with the opening slope D E and (2) that the posterior movement of the aortic root from Point 6 to Point 1 corresponds to the A wave *b* This echogram records the tilting discs of the aortic (D_A) and mitral valve (D_M) prosthesis Due to atrial fibrillation the dorsally directed motion from 6 to 1 is absent Note the small notch in the aortic root motion at the beginning of the isometric ventricular contraction (↑)

The echocardiographic examinations were carried out with a scope display echocardiograph unit manufactured by Organon Teknika with a Polaroid camera and Honeywell strip chart recorder with chart speeds of 25 50, and 100 mm/sec The ultrasound frequency was 2 25 MHz The transducer was placed in the second to fifth intercostal space (usually the third or fourth) 2 to 5 cm left parasternal A complete sector scan was made by the usual method and individual structures in differing intercostal spaces were separately recorded with the patients lying on their backs and the trunk elevated to approximately 30 degrees

ECGs and in most cases PCGs were simultaneously recorded routinely at the second left intercostal space parasternally Apexcardiograms or carotid pulse curves were also obtained

The results reported in this study were found to be reproducible by different examiners and independent of age and sex of the patients

Results

During sinus rhythm six points in the parallel echo curves of the anterior and posterior walls of the aortic root can be regularly identified in patients with aortic valve prostheses (see Fig 1b) In contrast in patients with normal aortic valves, it is frequently impossible to determine Points 2 and 3—opening and closing of the aortic valve—with accuracy [5] This accounts for the impression that there is a correlation between the time course of the ventral movement of the aortic root and the mechanical systole of the left ventricle [1,8] The two representative examples in Fig 1 show that the motion of the aortic root in the direction of the anterior thorax wall definitely continues beyond closure of the valve It is also clear that the posteriorly directed aortic root motion does not begin (Point 4) until after the second heart sound The steepest part of the aortic root curve is that between Points 4 and 5 thereafter a plateauing occurs At Point 6 (immediately after the P wave in the ECG) the aortic root accelerates again in the direction of the posterior chest wall until Point 1 is reached The course of the curve between Points 1 and 2 is practically horizontal whereby a small wave can occasionally be noted concomitantly with sets 1 and 2 of the first heart sound (mainly at the posterior wall of the aortic root)

The objective was thus to correlate the motion of the aortic root not only with the ECG and the PCG but also with the carotid pulse curve (CP) the apexcardiogram (ACG) and the echocardio-

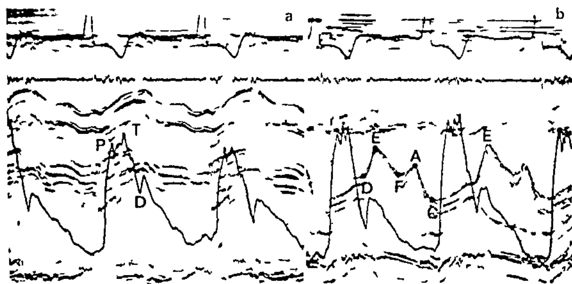


Fig 2 a and b ECG and PCG tracings (right parasternal second intercostal space) *a* echogram of the aortic root and *b* echogram of the anterior mitral valve leaflet recorded simultaneously with the carotid pulse curve *P* = percussion wave *T* = tidal wave *D* = dicrotic notch For details see text

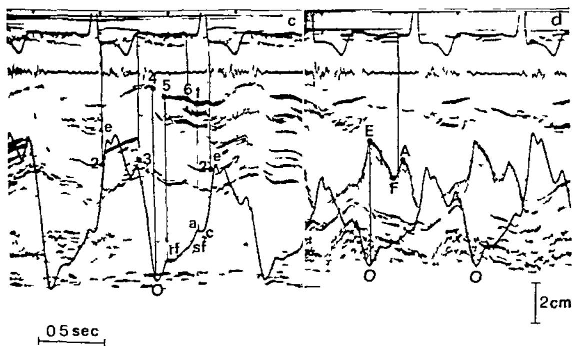


Fig 2 c and d ECG and PCG tracings (right parasternal second intercostal space) *c* echogram of the aortic root and *d* echogram of the anterior mitral valve leaflet recorded simultaneously with the apexcardiogram c = beginning of left ventricular contraction *e* = beginning of left ventricular ejection period *O* = mitral valve opening time *rf* = rapid filling wave *sf* = slow filling wave *a* = wave in response to atrial contraction For details, see text

Fig 5 The influence of contraction of the left atrium (complete AV block) on the echographic pattern of the aortic root *(a)* and the anterior mitral leaflet *(b)* See text for details

2 Point 5 indicates the end of the rapid filling phase

3 The posteriorly directed acceleration from Point 6 to Point 1 can only be clearly identified in patients with sinus rhythm (compare Figs 3a and 3b)

Fig 3b also shows that the small wave between Points 1 and 2 of the aortic root movement occurs during the isovolumetric phase of the left ventricle as the mitral valve has already closed at this point and the aortic valve has not yet been opened by the pressure rise in the left ventricle Final proof that the dorsal accelaration of the aortic root curve from Point 6 to Point 1 is only an expression of a change in volume in the left atrium after its contraction is supplied by Fig 4 A sinus rhythm prevails in the case of this patient with a Bjork Shiley prosthesis Each P wave (vertical lines) is followed by the previously mentioned dorsally directed motion of the aortic root. When a supraventricular extrasystole without atrial excitation occurs there is no dorsal displacement from Point 6 to Point 1 Also remarkable is the fact that a slow motion of the aortic root toward the anterior chest wall can be observed during the compensatory pause after the supraventricular extrasystole This finding is completely contrary to a hypothetical correlation between the ejection volume of the left ventricle and the ventral motion of the aortic root

The results previously obtained have included the finding that both walls of the aortic root are subject to presystolic dorsally directed motion apparently as a consequence of the contraction and the associated active emptying of the left atrium This would indicate that motion of the posterior wall of the aortic root is consistent with its anatomical juxtaposition and is due to the dorsally directed contraction of the anterior atrial wall counterpart of the simultaneous ventrally directed motion of the posterior wall of the left atrium (see Fig 1a) Consequently the parallel movement of the anterior wall of the aortic root should be regarded as purely passive If this hypothesis is correct changes in the volume of the left atrium will then influence the pattern of motion of the aortic root independently of the course of ventricular contraction

In order to investigate this possibility patients with complete AV blocks were echocardiographically examined Sections from a continuous echocardiogram or the aortic root (Fig 5a) and the mitral valve (Fig 5b) from each patient were superimposed in order to demonstrate the influence of atrial contraction on these two structures and to correlate timing As can be seen in Fig 5b an opening movement of the mitral valve (correlated with P waves No 1 3 5 7 8) or a change in the configuration of the E wave (P wave No 2) corresponds with each excitation and subsequent atrial contraction during the ventricular diastole If atrial contraction occurs during the ventricular systole however recognition of this finding in the pattern of motion of the mitral valve (P waves No 4 and 6) is precluded

On the other hand each contraction of the

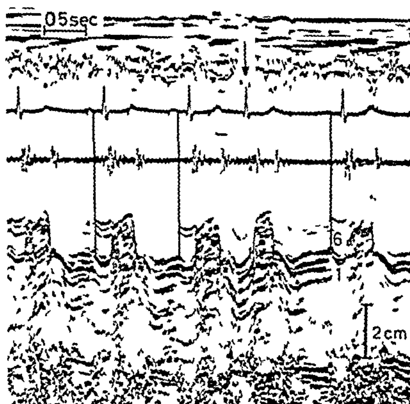


Fig 4 The typical posterior motion of the aortic root from Point 6 to Point 1 is noted at the end of each P wave this is absent in the case of a supraventricular extrasystole (↓) without atrial excitation

graphic movements of the mitral valve (Fig 2) A comparison of the time course of aortic root motion with the simultaneously recorded carotid pulse curve (Fig 2a) demonstrates that the characteristics of the two curves do not coincide at any time Two observations are of particular interest

1 Taking pulse wave speed into account it can be seen that at the time of the percussion wave (P) in the CP curve motion of the aortic root in the ventral direction has just begun

2 The ventral motion of the aortic root continues with the same slope even after the tidal wave (T) in the CP curve

Shortly after the second heart sound and the dicrotic notch (D) in the CP curve the aortic root begins to move toward the posterior chest wall (Point 4) This Point 4 would therefore appear to correspond with the opening motion (D E) of the mitral valve (Fig 2b) and to be directly before the 0 point of the ACG (Fig 2c) Fig 2c clearly shows that interruption of the steep movement of the aortic root toward the posterior chest wall (Point 5) coincides with the end of the rapid filling phase (rf) in the apexcardiogram The flat section of the aortic root curve from Point 5 to Point 6 reflects the slow filling phase (sf) of the ACG Point 6 then corresponds temporally with the end of the P wave in the ECG and with the beginning of the A wave of the anterior mitral leaflet (Fig 2d) The following aortic root motion toward the posterior chest wall is accompanied by contraction of the atrium The end of this coincides with the *a* wave in the ACG and with Point 1 of the aortic root curve In view of the coincidence of timing with the *c* point in the ACG the small wave at the posterior aortic root wall and before opening of the valve probably represents the isovolumetric course of contraction of the left ventricle in the echocardiogram

In a number of patients aortic and mitral valve motion was simultaneously recorded

In Fig 3a the aortic root motion was clearly identified in a patient with an aortic valve prosthesis and a normal mitral valve and in Fig 3b it was identified in a patient with both aortic and mitral valve prostheses

The tracings show

1 Point 4 coincides exactly with the opening movement of the mitral valve (DE)

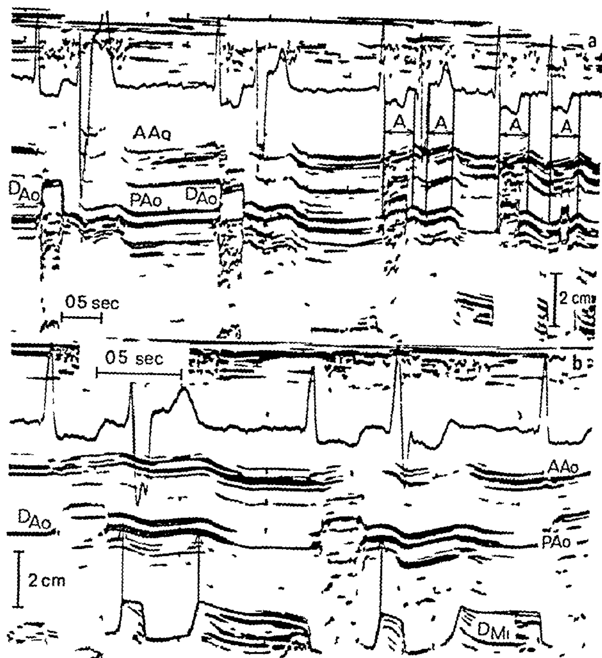


Fig 8 Echograms of the aortic root of a patient with a Bjork Shiley prosthesis in the aortic and mitral positions with atrial fibrillation and ventricular extrasystoles The early extrasystoles cause mitral valve closure but do not induce opening of the aortic valve *(b)* In spite of this the diastolic motion of the aortic valve is ventrally directed even after an extrasystole *(a* and *b)* The duration of this movement *(A)* is only slightly influenced by the left ventricular ejection period *(a)* *b* again shows that the diastolic posterior motion of the aortic root does not take place until after the mitral valve has opened (↓)

sequently the following clearly recognizable ventral displacement of the aortic root cannot be taken as an index of a displacement of volume from the ventricle to the aorta As can be seen at the right hand edge of Fig 8a the ventrally directed motion of the aortic root also appears to be little influenced in its amplitude and duration by the duration of aortic valve opening and by the ejection period of the left ventricle respectively

On the other hand this anterior aortic motion cannot represent the retrograde flow in the left atrium since the mitral valve is closed immediately on occurrence of the extrasystole as a result of the induced pressure rise in the left ventricle

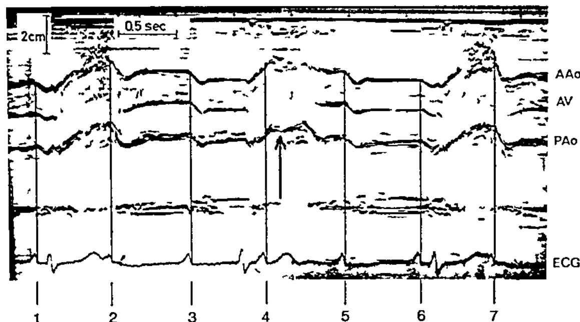


Fig 6 Echographic pattern of the aortic root (*AAo* = anterior wall *PAo* = posterior wall of the aortic root *AV* = aortic valve) of a patient with a complete AV block Note (↑) the interruption of ventral movement of the aortic root caused by atrial contraction Each following atrial contraction also influences the pattern of aortic motion.

atrium causes dorsally directed motion of the aortic root (P waves Nos 1 3 5 6 8) or acceleration of such motion (P waves Nos 2 7) regardless of the phase of ventricular excitation or contraction in which it occurs as is clearly shown by Fig 5a The echocardiographic pattern of the aortic root motion after the P wave No 4 in Fig 5a and Fig 6 also makes it apparent that atrial contraction can even interrupt the ventrally directed motion of the aortic root

The complete independence of the aortic root motion from the systolic ejection of the left ventricle into the aorta could be definitively demonstrated in a patient with a Bjork Shiley prosthesis and complete AV block (Fig 7) at the opening of the prosthetic disc the time of maximal flow in the aorta the aortic root does not move anteriorly but dorsally if atrial contraction occurs concomitantly (P waves No 1 and 3)

Finally Fig 5a (like Fig 1) also clearly shows that the anterior movement of the aortic root correlates with a flatter dorsally directed motion of the posterior wall of the left atrium This finding reflects the expected increase in volume of the left atrium during the ventricular systole

After having shown that a quantitative correlation between the effective systolic volume ejected by the left ventricle and the aortic root motion does not exist the influence of the ventricular systole on the echo pattern of the aortic root was examined

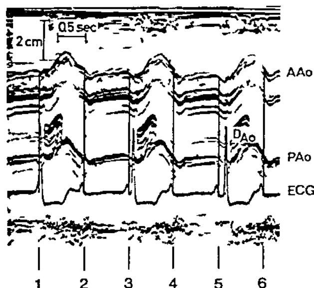


Fig 7 Echograms of the aortic root of a patient with a Bjork Shiley aortic valve prosthesis and complete AV block The aortic root motion is dorsally directed after the P waves 1 and 3 although the aortic valve has already been opened by ventricular contraction.

The echocardiograms of patients with ventricular extrasystoles (Fig 8a) demonstrate that the aortic valve (in this case prosthetic) does not open at all if the extrasystole occurs early Con

Decisive for our interpretation namely that there is no direct correlation between antegrade ejection and ventral aortic root motion are the findings which show the existence of such a motion after extrasystolic ventricular contraction *without* opening of the arotic valve (Fig 8) and on the other hand a dorsally directed movement of the aortic root when the aortic valve is already open in the case of coincidence of ventricular and atrial systoles (Figs 6 and 7)

In view of these findings the claim of Pratt and colleagues* that aortic root motion can be taken as an index of stroke volume is no longer tenable If changes in the amplitude of aortic root motion are to be taken as correlates of stroke volume (to be exact changes in the volume of left atrium) at all they can only be evaluated when it is certain that neither size nor compliance of the left atrium change This would in turn mean that the amplitude of aortic root motion can only be regarded as a sensitive parameter for assessing the ejection capacity of the left ventricle in acute experiments and with patients *without* mitral insufficiency or atrial septal defect

Summary

The movement of the aortic root under resting conditions was analyzed echographically in 82 patients (32 were postoperative examinations of Bjork Shiley arotic and/or mitral valve prostheses) Additionally ECG PCG carotid pulse curve or apexcardiogram were recorded simultaneously in the majority of the cases In view of the time correlation between these noninvasive parameters the results clearly show that both ventrally and dorsally directed motions of the aortic root during the cardiac cycle only reflect the change in volume of the left atrium Thus aortic root motion might if at all be an indir index of left ventricular stroke volume and or so if sinus rhythm is present and no mitr insufficiency or atrial septum defect exist

REFERENCES

1 Gramiak R and Shah P M Echocardiography of the aortic root Invest Radiol 3 ..8 1968
2 Gramiak R., and Shah P M Echocardiography of the normal and diseased aortic valve Radiology 96 1 197.
3 Goldberg B B Ultrasound measurement of the aortic arch right pulmonary artery and left atrium Radiology 101 383 1971
4 Feigenbaum H Echocardiography Philadelphia, 19.. Lea & Febiger Publishers
5 Feizi, O Symons C and Yacoub M Echocardiography of the aortic valve I Studies of normal aortic valve aortic stenosis aortic regurgitation and mixed aortic valve disease Br Heart J 36 341 1974
6 Francis G S Hagan A D., Oury J and O Raunke, R. A Accuracy of echocardiography for assessing aortic root diameter Br Heart J 37 376 1975
7 Gehrke J., Maldonado J Goh V., and Leeman S Neue echographische Beurteilungsmoglichkeiten der Aortenwurzel Hamodynamische Zusammenhange und klinische Bedeutung Z Kardiol Suppl 2 47 19 5
8 Pratt R C Parisi A F Harrington J J and Sasahara, A A The influence of left ventricular stroke volume on aortic root motion—an echocardiographic study Circulation 53 947 1976
9 Douglas J E and Williams G D Echocardiographic evaluation of the Bjork Shiley prosthetic valve Circulation 50 52 1974
10 Weyman A E., Dillon J C Feigenbaum H and Chang S Echocardiographic patterns of pulmonic valve motion with pulmonary hypertension Circulation 50 905 1974
11 Rushmer R F Cardiovascular dynamics Philadelphia, 1970 W B Saunders Company
12 Schlag W Wessel H J Biamino G and Schroder R. Ultraschallcharakteristik der Bjork Shiley Discus Prothese nach Aortenklappenersatz Zeitschr Kardiol Suppl 3 50 19 6
13 Strunk B L Fitzgerald J W Lipton M Popp R L, and Batty W H The posterior aortic wall echocardiogramm Its relationship to left atrial volume change Circulation 54 744 19 6

(Fig 8b) The ventral motion of the aortic root probably reflects only the antegrade pressure passive flow from the pulmonary system into the left atrium

Discussion

It has been reported that the two dominant echoes comprising the root of the aorta are probably the easiest of all cardiac echoes to record However this statement is contradicted by the lack of studies on the pattern of motion on this vascular structure which is automatically recorded echocardiographically in the course of assessing the functioning of aortic valves The cyclical motion of the aortic root was subdivided simply into a systolic movement towards the anterior thorax wall and a diastolic dorsally directed movement The cause of this motion was thought to be the course of contraction of the left ventricle either in the sense of a possible centrifugal effect or as the consequence of the effective antegrade ejected volume [1] Only the presystolic dorsally directed motion of both walls of the aortic root for example as shown in Figs 1 and 3 was attributed to the contraction of the left atrium since it is absent in the presence of atrial fibrillation [4]

The finding that the ventrally directed motion of the aortic root always continued beyond valve closure has been reported but not discussed in several papers [4-6] The lack of interpretation of this phenomenon may be due to the fact that the opening and closing motions of the aortic valve can only be recorded exactly in about 30% of normal cases and that multiple scarcely analyzable echoes between the aortic root limits are registered [5] in the case of diseased aortic valves particularly when stenosis is present

Confirming the conclusions of Strunk and associates [13] the results of our study clearly show that the diastolic pattern of the aortic root in the echogram corresponds exactly with the time course of the physiological changes in volume of the left atrium (Figs 2 3 4 and 5) The dorsally directed motion of the aortic root (Point 4) does not begin simultaneously with closure of the aortic valve (Point 3) but *always* begins with the DE slope of the anterior mitral leaflet This initially relatively steep motion flattens out (Point 5) at the end of the rapid filling phase of the left ventricle (rf) and then demonstrates repeated acceleration (Point 6) in concomitance with the A wave of the anterior mitral leaflet i e through atrial contraction finally reaching the lowest point Point 1 If atrial fibrillation occurs the acceleration wave from Point 6 to 1 is absent

The motion of the anterior aortic root wall which is parallel to the posterior must therefore be regarded as passive transmission of the motion of the anterior left atrial wall via the posterior aortic wall The reported larger amplitude of the maximal excursion of the anterior wall probably has no relation to an asymmetrical extension of the aortic wall during the ejection period but may be only the result of an oblique echo path and thus the expression of differing projections In this regard it is significant that no marked differences in the diameter of the aorta were detected throughout the entire cardiac cycle

If the entire diastolic motion of the aortic root is apparently correlated with the process of emptying of the left atrium into the left ventricle one must discuss to what extent the anterior systolic motion of the aortic root is also the expression of a change in volume of the left atrium in the sense of an increase in volume as physiologically expected during the left ventricular systole The primary finding in favor of this hypothesis is that the ventral motion of the aortic root is accompanied by a dorsally directed motion of the posterior wall of the left atrium which although not so pronounced can frequently still be clearly determined echographically (Figs 1a and 5a) Several of the findings presented in this study do not support the assertion that there may be a *direct* quantitative correlation between the stroke volume of the left ventricle and the amplitude and duration of the ventral motion of the aortic root [8] Even a comparison of the course of the carotid pulse curve or the apexcardiogram with the echocardiographic pattern of aortic root motion (Figs 2a and 2b) does not support the thesis that the stroke volume influences the movement of this vascular structure The tracing representing the ventral movement of the aortic root rises in fact constantly during the ejection period independently of the maximal aortic flow and volume changes expected during the upstroke of the carotid pulse curve to the percussion wave or to the e wave in the apexcardiogram The slope of the aortic root motion curve declines only slightly when the aortic valve has closed

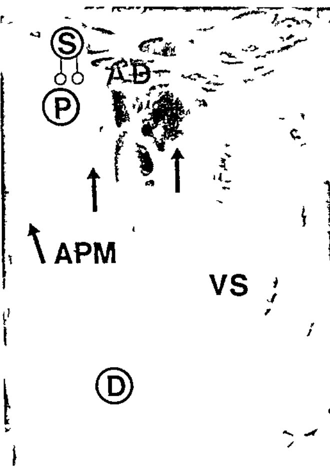


Fig 1 Photograph of an infarcted tissue preparation dissected from the left ventricle of a dog 24 hours after ligation of the left anterior descending coronary artery *Arrows* indicate the demarcation between normal tissue *above* which appears dark and infarcted tissue *below* which appears pale *VS* indicates the ventricular septum *APM* is the anterior papillary muscle and *AD* is the anterior division of the left bundle branch which is a free running false tendon *P* and *D* indicate the approximate locations of the proximal and distal recording sites respectively and the position of the extracellular stimulating electrodes is indicated by *S*

reductions of resting membrane potential and of action potential amplitude and maximum velocity of phase 0 depolarization Action potential duration was increased as was the duration of the refractory period Impulses propagating in infarcted regions exhibited slowing of conduction and unidirectional block and reentry were demonstrated Enhanced automaticity was also observed It was postulated that these abnormal electrophysiological properties might form the basis of at least some of the ventricular arrhythmias which commonly complicate acute myocardial infarction

The effects of a drug lidocaine on the abnormal Purkinje fibers surviving in infarcted regions were subsequently studied by Allen and colleagues[21] who found that the drugs effects on such cells were different from what would have been predicted based on knowledge of its effects on normal cells Other investigators using a variety of drugs on cardiac tissues depressed by means other than acute myocardial infarction have also found that abnormal tissues may respond to drugs differently than do normal tissues[2, 23]

It is conceivable therefore that the abnormal Purkinje fibers surviving in infarcted regions might respond to digitalis differently than do normal fibers and that patients or animals with acute myocardial infarction might be susceptible to toxic arrhythmias on this basis In the present study we have tested this hypothesis using microelectrode techniques in vitro on tissue preparations obtained from infarcted canine hearts identical to those used by Friedman and Allen and their co workers[17, 18, 20, 21]

Methods

Myocardial infarction was produced in previously healthy adult mongrel dogs weighing 10 to 15 kilograms by ligating the left anterior descending artery under general anesthesia with intravenous sodium pentobarbital (30 mg/kg) using previously described techniques[17] The animals were allowed to recover from the anesthesia and then approximately 24 hours later the survivors were reanesthetized with sodium pentobarbital (15 to 30 mg/kg) and the hearts were rapidly excised and dissected in cooled oxygenated Tyrodes solution the composition of which has been described previously[1] The portion of the left ventricle comprising the anterior half of the interventricular septum and the paraseptal free wall with attached anterior papillary muscle was dissected free of other tissue and was pinned endocardial surface up to the wax base of a tissue bath (volume 50 ml) and superfused with Tyrodes solution at 20 ml/minute The dissection procedure has been described in detail elsewhere[7] The apical half to two thirds of the tissue preparations was infarcted but the basal portion including the tip of the anterior papillary muscle and the attached anterior division of the left bundle branch was invariably spared (Fig 1) Differentiation between normal and infarcted tissue was easily accomplished by gross inspec

Effects of ouabain on the electrophysiological properties of subendocardial Purkinje fibers surviving in regions of acute myocardial infarction

F James Brennan M D
James R Bonn M D
Kingston Ontario Canada

The belief that patients with acute myocardial infarction have enhanced susceptibility to the toxic effects of digitalis is widespread and is based primarily on animal studies which have consistently demonstrated that toxic arrhythmias develop at lower doses of digitalis in animals with experimental acute myocardial infarction than in normal animals [1] The clinical evidence supporting this concept is anecdotal and tenuous however [5-7] and there have been several clinical studies in which no evidence of enhanced toxicity of digitalis in patients with acute myocardial infarction was found [8-10] Nevertheless recent review articles and widely used current reference sources continue to indicate that patients with acute myocardial infarction have enhanced susceptibility to the toxic arrhythmias of digitalis [11]

The electrophysiological mechanisms responsible for arrhythmias occurring as a complication of digitalis toxicity have been extensively investigated using microelectrode techniques (for Reviews see references 14 and 15) A study carried out by Rosen and co workers is of particular interest since it correlated in vivo electrocardiographic evidence of digitalis toxicity with in vitro intracellular microelectrode recordings using an experimental preparation in which Purkinje fibers excised from a dog s heart were perfused in a tissue bath with blood from a living donor dog They demonstrated that the appearance of toxic arrhythmias in the donor dog s heart during ouabain infusion was associated with decreases in action potential amplitude resting membrane potential maximum rate of phase 0 depolarization and action potential duration of the simultaneously recorded Purkinje fiber transmembrane potentials and slowing of conduction velocity In some experiments automaticity due to phase 4 depolarization was enhanced In others automaticity was enhanced due to the occurrence of oscillatory afterpotentials (which Rosen and associates referred to as low amplitude potentials) Such oscillatory afterpotentials have also been observed by many other investigators in recent years and are now believed to play an important role in the genesis of digitalis arrhythmias [4, 15]

Most of the investigation into the cellular electrophysiological correlates of digitalis toxicity including the work of Rosen and associates cited above has been conducted on normal cardiac tissues In acute myocardial infarction however cellular electrophysiological properties are altered by the disease process The alterations which occur during the most acute phases of infarction are poorly understood at present but those which persist beyond 24 hours have been studied in detail [6] Friedman and coworkers [7, 8] found that canine subendocardial Purkinje fibers surviving in infarcted regions 24 to 72 hours after coronary artery ligation exhibited

F om the Departm nts of Med cine and An esthesiology Queen s Uni ers ty Kingston Ontario C n d

Supported by th Ont rio Heart Fou dation

Recei ed for publicati n Ja 31 19 9

Accepted for publ cat n M y 21 1979

Reprint requests Dr F J Bre n n D vis n f C rdiology D pt of Medici e Queen s University Kingston Ontari Can d K L 3N6

000? 8 03/80/080?01 + 1 $01 ?0 0 19?0 The C V Mosby Co

'able I Effects of ouabain on transmembrane resting and action potential characteristics

	Proximal site			*Distal site*		
	Normal preparations	*Infarcted preparations*	*P*,	*Normal preparations*	*Infarcted preparations*	*P*
1DP (mV)						
Control	83 0 ± 1 5	83 6 ± 1 1	NS	88 0 ± 1 7	78 6 ± 2 7	<0 05
Ouabain 2 5 × 10 M	82 , ± 1 8	82 9 ± 6 8	NS	83 4 ± 2 3	77 5 ± 2 0	NS
P,	NS	NS		NS	NS	
Amp (mV)						
Control	121 5 ± 2 5	118 8 ± 1 7	NS	122 6 ± 2 6	11?? ± 4 9	NS
Ouabain 2 5 × 10 M	118 3 ± 2 7	114 2 ± 4 4	NS	121 3 ± 4 0	107 5 ± 4 4	NS
P,	NS	NS		NS	NS	
V_m (V/sec)						
Control	503 3 ± 31 4	449 2 ± 22 5	NS	41?0 ± 34 7	3,4? ± 43 2	NS
Ouabain 2 5 × 10 M	497 7 ± 70 8	437 0 ± 4? 8	NS	446 2 ± 91 9	3?3 3 ± 34 9	NS
P	NS	NS		NS	NS	
AI D (msec)						
Control	23? 8 ± 16 ,	219 3 ± 7 9	NS	211 4 ± 15 5	2?7 4 ± 11 3	NS
Ouabain 2 5 × 10 M	22,2 ± 9 0	212 3 ± 11 6	NS	201 8 ± 9 3	236 1 ± 16 2	NS
P	NS	NS		NS	NS	
APD (msec)						
Control	3,8 8 ± 16 2	374 0 ± 9 2	NS	331 4 ± 20 8	43?? ± ?1 0	< 0 05
Ouabain 2 5 × 10 M	36,2 ± 15 4	387 3 ± 1,7	NS	338 2 ± 16 0	46?5 ± 21 3	< 0 01
P	NS	NS		NS	< 0 01	

All values ar m an ± SEM obtained from five normal preparations and eight infarcted preparations P indicates the significance of the diff renc between mean control v l es and m an values obtained during expo ure to ouabain 2 5 × 10 M while I indi ates the sign ficance of the diff renc between the mean val ies obtained at a given te in normal preparati ons and the mean values at the same site in infarcted preparation MDI = maximum dia tolic p tential Amp = action potential amplitud V = maximum rate of d polarization of phase 0 APD an APD = acti on potential duration to 50% and 100% repolarizat on re pecti ely

by *measuring the distance between the onset of* the action potential upstrokes at the two sites Then with the transmembrane potentials being recorded continuously on moving film premature stimuli were introduced at progressively shorter coupling intervals after every eighth basic drive stimulus The intervals between the responses to the basic drive and premature stimuli at the proximal site (P_1P) and the distal site (D_1D) were determined until excitation of the subendocardial Purkinje fibers at the proximal site failed due to absolute refractoriness of those cells The effective refractory period was defined as the shortest P P interval at which conduction to the distal site was successful while the functional refractory period was the shortest D_1D_2 interval achieved The absolute refractory period of the cells at the proximal site was the minimum P_1P_2 interval achieved

In some experiments as the coupling interval of basic and premature stimuli (S S) was decreased the P P_2 interval decreased pari passu up to a point *then increased Because of the very* short distance between the stimulating electrode pair and the microelectrode at the proxima recording site we felt it was unlikely that th phenomenon was due to conduction dela between the stimulating and proximal recordin sites but was probably due to indirect activatio of the Purkinje fibers at the proximal site via th underlying muscle P_1P_2 and D_1D_2 interval recorded under such circumstances were dis carded In those experiments the effective refrac tory period was still the shortest P_1P_2 interval a which conduction occurred to the distal site bu the functional refractory period was the shortes D_1D interval achieved before latency develope between the stimulating and proximal recordin sites

3 Spontaneous activity While transmem brane potential was being simultaneously record ed from subendocardial Purkinje fibers at bot the proximal and distal sites the basic driv stimuli were abruptly terminated for approx mately 10 seconds The occurrence of sponta neous action potentials during the interruption o *driving stimuli* was noted if it occurred and th sequence of activation at the proximal and dista

tion—a method which has been validated by others.[17] For control studies anatomically identical tissue preparations were prepared from the hearts of normal dogs.

The superfusate was equilibrated with 95% O_2, 5% CO_2 and maintained at a temperature of 36 ± 1° C. Its potassium concentration was 4.0 mM in all experiments.

All preparations were stimulated extracellularly at a cycle length of 800 msec via Teflon insulated bipolar silver electrodes located on the non-infarcted tip of the anterior papillary muscle. Basic drive stimuli (S_1) were rectangular pulses 2 to 3 msec in duration and 1 to 2 times diastolic threshold in amplitude. For experiments in which conduction of premature beats and refractory periods were measured, premature impulses were delivered via the same electrode pair at selected intervals after S_1. The premature stimuli (S_2) were rectangular pulses 2 to 3 msec in duration and >5 times diastolic threshold. All stimuli were isolated from ground. Transmembrane potentials were recorded through glass microelectrodes filled with 3 M KCl with tip resistances of 10 to 20 megohms. The microelectrodes were coupled via a silver-silver chloride electrode to a preamplifier with high input impedance (1.5×10^{9} ohms) and capacitance neutralization.* The output of this preamplifier was displayed on oscilloscopes (Tektronix models 5433 and 5103N) and was photographed with oscilloscopic cameras (Grass model C4 and Tektronix model C5A, respectively). The maximum rate of depolarization of action potentials was determined by electronic differentiation as described by Bigger and co-workers.[24]

In all experiments subendocardial Purkinje fibers were impaled at two sites, a proximal one on the tip of the papillary muscle within 1 mm of the insertion of the false tendon carrying the anterior division of the left bundle branch and a distal site on the apical portion of the preparation below the insertion of the papillary muscle (Fig. 1). In all preparations the proximal site was within 2 mm of the stimulating electrode pair and was in normal tissue even in the tissue preparations with infarcts. The distal site was well within the infarcted region in infarcted tissue preparations, whereas in the non-infarcted preparations it was, of course, in normal tissue. All control observations were made after an equilibration period of at least 2 hours following dissection and mounting and during which the tissue preparation was driven regularly at a cycle length of 800 msec and was superfused as described above. Ouabain was then added to the superfusate in a concentration of 2.5×10^{-8} M and observations were repeated after exposure to the drug for between 90 and 120 minutes. The concentration of ouabain was lower than generally used in studies of toxicity. Preliminary experiments, however, had shown that conventional toxic doses of the drug caused the tissue preparations to rapidly develop spontaneous activity to such a degree that it was impossible to drive the tissue regularly and so to repeat during drug exposure the protocol which had been followed in the control period. By trial and error, a dose was selected which caused toxic manifestations to develop sufficiently slowly so that this problem was circumvented.

The experimental observations fell into three categories.

1. **Transmembrane resting and action potential characteristics.** Between five and 10 subendocardial Purkinje fibers were impaled consecutively at both the proximal and distal sites and photographic records were made of the transmembrane resting and action potential characteristics of each cell. At the two sites, all impalements were made within a 1 sq. mm. area. This procedure was repeated during exposure to ouabain. Data obtained from individual cells was pooled to give average values of the various transmembrane potential parameters for the two sites under control conditions and during drug exposure. These averaged data were then subjected to statistical analysis. It was necessary to make multiple impalements and use averaged data for analysis because movement of the tissue preparations, particularly during exposure to ouabain, rendered it impossible to maintain continuous impalements of single cells.

2. **Refractoriness and conduction.** Two cells were impaled simultaneously, one at each site. The two transmembrane potential recordings were displayed simultaneously on an oscilloscope. With the tissue being driven at a constant cycle length of 800 msec, photographs were made of the simultaneously displayed action potential upstrokes recorded at a rapid sweep speed (1 cm./5 msec.). Conduction time was determined

*Constructed by M. S. Ross, Department of Pharmacology, Columbia University, New York.

Table II Effects of ouabain on conduction and refractoriness

	Conduction time		*Absolute refractory period (proximal site)*		*Effective refractory period*		*Functional refractory period*	
	Control	*Ouabain 2 5 × 10 M*	*Control*	*Ouabain 2.5 × 10 M*	*Control*	*Ouabain 2 5 × 10 M*	*Control*	*Ouabain 2.5 × 10 M*
Normal preparations	8 12 ± 1 2	7 2 ± 1 3	297.5 ± 20 6	310 ± 23 5	297 5 ± 20 6	310 ± 23 5	297 5 ± 18 9	315 ± 19 4
Infarcted preparations	14 0 ± 1 6	10 3 ± 1 4	311 7 ± 16 6	331 7 ± 12 8	333.2 ± 12 3	338 3 ± 11 7	356 7 ± 20 4	351 7 ± 19 7
P	< 0 05	NS	NS	NS	NS	NS	NS	NS

All values are mean ± S E M expressed in millisecond Results were obtained from experiments in five normal preparations in infarcted preparations conduction time was measured in 10 experiments and refractory periods in six The significance of the difference in mean values for a given parameter between normal and infarcted preparations is indicated by P Asterisks indicate the significance of the difference between mean values obtained before and during exposure to ouabain in a given type of preparation (= P < 0 05 = P < 0 01) NS = not significant

rations values for MDP Amp and V_m at the distal site were similar to those recorded at the proximal site Although values for APD_5 and APD_{100} were respectively 9 2% and 12 5% less at the distal site than at the proximal site these differences were not significant On the other hand in infarcted preparations the maximum diastolic potential and action potential amplitude were significantly reduced and APD 0 was significantly prolonged at the distal (infarcted) site when compared with the distal site in normal preparations The prolongation of APD_1 was sufficiently great that action potentials recorded at the distal site in infarcted preparations were longer in duration than those recorded at the proximal site the reverse of the situation observed in normal preparations This prolongation was due primarily to a decrease in slope of phase 3 of the action potential since APD 0 while slightly prolonged was not significantly so

In both types of preparation ouabain 2 5 × 10 M caused no change in MDP Amp APD_{50} and V_m at the distal site In normal preparations the drug also did not affect APD 00 but in infarcted preparations it caused significant further prolongation of APD_{100} by 6 8 ± 2 0% (mean ± S E M p < 0 01) Thus the discrepancy which existed under control conditions between the proximal and distal sites in the infarcted preparations with respect to APD was increased by the addition of the drug

2 Effects of ouabain on conduction and refractoriness (Table II) Under control conditions the conduction time of basic drive impulses from the proximal to the distal site was significantly longer in infarcted than in normal preparations Ouabain caused no change in normal preparations but in infarcted preparations the drug decreased conduction time by 22 ± 9% (p < 0 05) (Fig 2)

Prior to superfusion with ouabain premature impulses introduced near the proximal site conducted rapidly to the distal site in normal preparations and there was little increase in conduction delay as the coupling interval between the basic drive and premature impulses was progressively decreased This was presumably because action potential duration at the distal site was shorter than at the proximal site so that a premature impulse introduced at the proximal site would encounter progressively less refractory tissue as it propagated distally [18] For the same reason conduction block never occurred between the proximal and distal recording sites Thus there was no significant difference in these preparations between the absolute refractory period of cells at the proximal site the effective refractory period and the functional refractory period Following superfusion with ouabain 2 5 × 10 M for 90 minutes there was modest prolongation of all refractory periods but this achieved statistical significance only for the functional refractory period

In infarcted preparations unlike normal preparations premature impulses encountered progressively more refractory tissue as they propagated distally Thus as the coupling interval between basic drive and premature impulses was decreased conduction time of the premature impulses from the proximal to the distal site

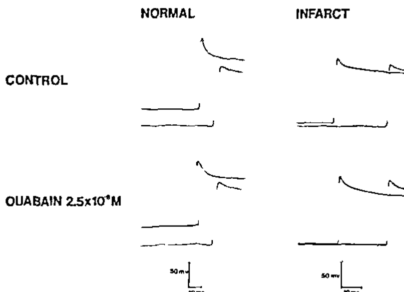


Fig 2 Effect of ouabain on conduction time between the proximal and distal recording sites in a normal preparation *(left panels)* and an infarcted preparation *(right panels)* The preparations were being driven at a cycle length of 800 msec In each panel transmembrane potential recordings are displayed from two Purkinje fibres one at the proximal and one at the distal site In the normal preparation the resting membrane potentials of the two cells have been separated vertically while in the infarcted preparation they have been superimposed In the normal preparation *(left panels)* conduction time between the two sites was 8 6 msec under control conditions After exposure to ouabain 2 5 × 10 M for 90 minutes the conduction time was virtually unchanged at 8 ? msec In the infarcted preparation *(right panels)* on the other hand conduction time decreased from 24.5 msec during the control period to 20 0 msec after exposure to the same concentration of ouabain for the same period of time

sites was also observed The transmembrane potential readings were carefully examined for the presence of oscillatory afterpotentials following the last driven impulse and also for the presence of phase 4 depolarization during and after cessation of pacing

In the experiments in which the effects of ouabain on refractoriness and conduction and on spontaneous activity were studied continuous impalements were not maintained throughout the experiments When a microelectrode became dislodged from a cell it was replaced in another cell within the 1 mm ^{2} confines of the proximal or distal site

Statistical analysis was carried out using Student s t test for comparing means of non independent samples to assess the significance of any change observed at a given site or in a given type of preparation (normal or infarcted) To compare data obtained from different sites or different types of preparation the t test for comparing means of independent samples was used A p value of less than 0 05 was considered significant

Results

1 Effects of Ouabain on Transmembrane Resting and Action Potential Characteristics

Proximal site (Table I) In both normal and infarcted preparations the proximal site was in a region of normal tissue Under control conditions there was no difference between infarcted and normal tissue preparations with respect to maximum diastolic potential (MDP) action potential amplitude (Amp) action potential duration to 50% and 100% repolarization (APD_{50} and APD_{100} respectively) and maximum upstroke velocity of phase 0 (V_{max}) of the action potential of subendocardial Purkinje fibers at the proximal site The addition of 2 5 × 10 M ouabain to the perfusate resulted in no significant change in any of these parameters

Distal site (Table I) In infarcted preparations the distal site was in the infarcted region while in normal preparations it was in normal tissue Prior to drug superfusion differences were observed at the distal site between the two types of preparation with respect to transmembrane resting and action potential characteristics In normal prepa

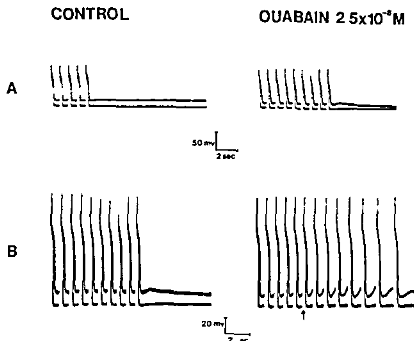


Fig 4 Ouabain induced oscillatory afterpotentials (OAP) *A* and *B* are from two different experiments conducted on infarcted tissue preparations In each panel the upper trace is the transmembrane potential recording from a subendocardial Purkinje fiber at the distal (infarcted) site and the lower trace is from a fiber at the proximal (normal) site In experiment A during control a stable resting membrane potential was attained and maintained at each site following cessation of pacing After exposure to ouabain a stable resting membrane potential again followed the cessation of pacing at the proximal site but a single low amplitude OAP was observed at the distal site following the last driven action potential In *B* there was a single low amplitude OAP at the distal site following the last driven response even during the control period Following exposure to ouabain the last driven action potential *(arrow)* was followed by several OAP of large amplitude These were initially of sufficient magnitude to bring the transmembrane potential to threshold resulting in action potentials which propogated from the distal to the proximal site The amplitude and rate of depolarization of the OAP progressively decreased and the cycle length progressively increased until there was failure to reach threshold Both during control and following ouabain the cell at the proximal site exhibited a stable resting membrane potential during phase 4

site where the slope was about 2 5 mv /sec

The eighth infarcted preparation exhibited a single oscillatory afterpotential at the distal site following cessation of pacing during the control period while at the proximal site a stable resting membrane potential occurred Following exposure to ouabain variable spontaneous diastolic depolarization was evident only at the distal site during pacing and when pacing was interrupted several oscillatory afterpotentials of sufficient magnitude to reach threshold and initiate action potentials occurred at the distal site These action potentials propagated to the proximal site where resting membrane potential remained stable during phase 4 (Fig 4*B*)

Discussion

The transmembrane resting and action potential characteristics of subendocardial Purkinje fibers and the functional properties of the subendocardial Purkinje fiber network which we observed under control conditions in both normal and infarcted preparations were generally similar to those which have been reported previously by other investigators [17 1] There were some minor differences however In normal preparations we found that although the duration of action potentials at the distal site was shorter than at the proximal site the difference was not statistically significant Others have found distal Purkinje fiber action potentials to be significantly shorter in duration than proximal action potentials [17 1 21] This discrepancy is probably due to the small number of experiments conducted on normal preparations in the present study since the mean values for APD_{50} and APD at both the proximal and distal sites were similar to those reported by others [17 19 1] In infarcted regions it has been previously reported that action potential duration is prolonged and resting membrane

increased and in two of six experiments there was conduction block between the two sites (Fig 3) In these preparations therefore the mean effective refractory period was longer than the absolute refractory period of the cells at the proximal site and the functional refractory period considerably exceeded the effective refractory period Ouabain caused prolongation of all three refractory periods the magnitude of which was statistically insignificant when compared with control values however (Fig 3)

3 Effects of ouabain on spontaneous activity *In five normal preparations the basic drive train* of impulses was abruptly interrupted for 10 seconds during the control period In each case following the response to the last driven impulse the fibers at both the proximal and distal sites attained and maintained a stable resting membrane potential during the entire 10 second interruption and no undriven action potentials occurred An identical response was observed in every preparation when pacing was interrupted after 90 minutes of exposure to ouabain 2.5×10^{-8} M

The response to 10 second interruptions of basic drive impulses was also studied in eight infarcted preparations In seven of these preparations a stable resting membrane potential was maintained at both the proximal and distal sites following the last driven action potential and no spontaneous activity was observed during the interruption of pacing during the control period After exposure to ouabain the response was the same in two of these preparations In two additional experiments although a stable resting membrane potential occurred at both sites during the suspension of pacing several spontaneous action potentials occurred at progressively longer cycle lengths after the last driven response Each undriven response resulted in activation initially at the distal site followed after a brief interval by activation at the proximal site indicating that the impulses probably originated within the infarct In two more experiments following cessation of pacing after exposure to ouabain no spontaneous action potentials occurred but a single oscillatory afterpotential was observed at the distal site while at the proximal site a stable resting membrane potential followed the last driven response (Fig 4A) In the seventh preparation a stable spontaneous rhythm with a cycle length of 80? msec and with activation at the distal site preceding the proximal site occurred after exposure to ouabain In this experiment stable phase 4 depolarization was evident at both sites after exposure to ouabain this was more marked at the distal site where the slope was approximately 5 mv/sec than at the proximal

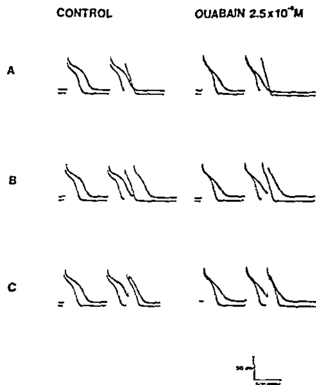


Fig 3 Effects of ouabain on the conduction of premature impulses in an infarcted tissue preparation In each panel the upper trace is recorded from a cell at the distal (infarcted) site and the lower trace is from a cell at the proximal (normal) site *The left hand panels* were recorded under control conditions while those on the *right* were obtained after exposure to ouabain 2.5×10^{-8} M for 90 minutes. The first two action potentials in each panel are responses to basic drive stimuli at a cycle length of 800 msec and the third action potential is the response to a premature stimulus. *A* shows the response to the earliest premature impulse which resulted in activation at the proximal site (absolute refractory period ARP) *B* shows the earliest premature response which conducted successfully to the distal site (effective refractory period ERP) and *C* shows the earliest obtainable premature response at the distal site to a premature impulse delivered near the proximal site (functional refractory period FRP) The ARP was 300 msec during control and 290 msec after ouabain The ERP was 320 msec under control conditions and 330 msec after ouabain These values differed from the ARP values because there was conduction block between the proximal and distal sites of the earliest premature responses both before and during exposure to ouabain *(panel A)* The FRP decreased from 400 msec during control to 380 msec after ouabain. Both under control conditions and during exposure to ouabain the FRP considerably exceeded the ERP because there was marked conduction delay of early premature responses (compare panel B with panel C) The changes in ARP ERP and FRP after ouabain were not significant.

velocity and failed to increase the functional refractory period in infarcted preparations unlike its effects in normal preparations It might have been expected that the prolongation of action potential duration in infarcted regions induced by ouabain would have resulted in prolongation of the functional refractory period of infarcted preparations of even greater magnitude than occurred in normal preparations The fact that this did not occur can be explained by the improvement in conduction which was observed Why conduction improved is not certain There are many possibilities including a change in the slope of the membrane responsiveness curve a reduction of the threshold voltage or alterations of the passive electrical properties of the Purkinje fibers making up the conduction pathway It cannot be explained by the observed effects of ouabain on transmembrane resting and action potential characteristics in the regions studied but since these characteristics of Purkinje fibers surviving in infarcted regions are very non uniform[17] and since we only studied minimally depressed areas it is also possible that ouabain had effects on transmembrane resting and action potential characteristics of more depressed parts of the conduction pathway which would result in improved conduction such as an increase in amplitude or V_m Finally, it is possible that phase 4 depolarization or oscillatory afterpotentials occurring in infarcted regions could facilitate conduction by bringing the transmembrane potential closer to the threshold potential[30]

In the present study there were also differences between normal and infarcted preparations with respect to the effects of ouabain on spontaneous activity While there was no effect on any of the normal preparations some form of spontaneous activity occurred in response to ouabain in six of the eight infarcted preparations studied Stable phase 4 depolarization was observed in one preparation more marked in the infarcted region than in the normal one and oscillatory afterpotentials were observed in the infarcted region in an additional three experiments In the other two experiments spontaneous activity was manifested by the occurrence of several unstimulated beats at progressively increasing cycle lengths following the cessation of pacing but the mechanism giving rise to these unstimulated responses was unclear since transmembrane potential was stable during phase 4 at both recording sites in these preparations

Enhancement of phase 4 depolarization and the development of oscillatory afterpotentials are two well recognized mechanisms by which digitalis may induce spontaneous activity in Purkinje fibers[14,15] The appearance of either of these phenomena has been reported to correlate well with the appearance of ventricular tachyarrhythmias in dogs given toxic doses of digitalis[16] The factors influencing the appearance of one or the other form of spontaneous activity are not well understood but Rosen and associates[31] found that enhancement of phase 4 depolarization tended to appear more readily in damaged tissue or in the presence of a low concentration of potassium in the superfusing solution whereas oscillatory afterpotentials tended to occur in normal tissues superfused with solutions having a potassium concentration of 4 to 5 5 mM[31] Our observations are in agreement with theirs in that in the minimally depressed areas we studied within infarcted regions (average resting membrane potential = 78 6 mv) and with superfusion with modified Tyrode s solution having a potassium concentration of 4 0 mM oscillatory afterpotentials were observed more commonly than enhanced phase 4 depolarization It must be noted that whenever oscillatory afterpotentials were observed they occurred only in the infarcted region and that when phase 4 depolarization occurred it was more marked in the infarcted than in the normal region

It is tempting to speculate on the possible clinical significance of our observations In theory the effects of ouabain on spontaneous activity could be responsible for the appearance of toxic arrhythmias in an infarcted heart at a concentration of the drug which would be well tolerated by a normal heart On the other hand the observed improvement of conduction caused by ouabain in infarcted tissue preparations without a concomitant change in the functional refractory period would in theory tend to prevent or abolish arrhythmias due to reentrant mechanisms in infarcted hearts[3] We feel however that any attempt to extrapolate our results in this manner must be made with extreme caution It requires the assumptions that subendocardial Purkinje fibers survive in regions of acute myocardial infarction in man as in dogs that the surviving fibers have similar electrophysiological properties in the two species in vitro and in vivo that the electrophysiological properties respond to digitalis in a similar manner and that the concentration

potential action potential amplitude and V_m are variably depressed when compared with anatomically similar regions of noninfarcted hearts[17, 19, 21] Our observations are in agreement although because of a large standard deviation the depression of V_m was not statistically significant

It should be noted that within the infarcted region we selected as the distal recording site an area in which resting membrane potential was not severely depressed and in which spontaneous diastolic depolarization was not evident when the preparation was being driven at a cycle length of 800 msec during the control period This was done for two reasons Firstly it has been reported previously that in 24 hour infarcts regions exhibiting severely depressed resting membrane potentials (i e less than −73 mv) do not maintain stable transmembrane resting or action potential characteristics over periods of several hours and hence would have been unsuitable for the present type of study[21] Secondly within the infarcted regions of different tissue preparations we wished to select areas with roughly similar baseline electrophysiological properties for study We recognize that the areas studied were not representative of the entire infarcted region in that they were undoubtedly less depressed than the infarcted region as a whole

It is well known that many hours of exposure to ouabain are required before a steady state is reached, and that inotropic effects occur long before any changes are demonstrable in transmembrane resting and action potential characteristics of normal mammalian ventricular myocardial cells and Purkinje fibers[2] The initial electrophysiological effect in normal Purkinje fibers has been reported to be prolongation of the action potential[2] and to our knowledge this effect has not been observed in normal mammalian Purkinje fiber preparations exposed to a concentration of ouabain as low as 2 5 × 10 M for less than 5 hours when the preparations have been driven at cycle lengths of 800 msec or more—i e under the conditions of this study Significant inotropic effects have been observed under these conditions however Thus we believe the effects of ouabain observed in this study correspond to the effects of a therapeutic concentration of the glycoside We recognize that the observations were made before a steady state was achieved and that more dramatic effects would probably have been seen after longer exposure to the drug

It is not surprising therefore that in the present study there was no effect of ouabain on transmembrane resting and action potential characteristics of subendocardial Purkinje fibers in normal preparations and in normal regions of infarcted preparations or on the conduction velocity and the effective refractory period in normal preparations Despite this there was significant prolongation of the functional refractory period of normal preparations The mechanism for this effect is not clear The functional refractory period depends on both the refractory properties of the individual cells forming the conduction pathway and on the many other factors which determine the velocity and safety factor of conduction along the pathway such as membrane responsiveness threshold for excitation and the passive electrical properties of the conducting cells We are not able to state which of these determinants were altered by ouabain or to what extent It is apparent however that prolongation of the functional refractory period of normal Purkinje fibers is a more sensitive electrophysiological indicator of digitalis effect than is prolongation of the action potential duration a fact which has not been reported previously

Within infarcted regions the effects of ouabain on surviving subendocardial Purkinje fibers differed from the effects on normal fibers in anatomically similar locations of normal noninfarcted hearts As in normal preparations the drug caused no change in the resting membrane potential or in the amplitude and rate of rise of the action potential upstroke of the abnormal fibers in infarcted regions and no change in the effective refractory period of the infarcted preparations It did however, cause significant prolongation of the action potential duration of fibers in infarcted regions As previously noted prolongation of the action potential duration has been reported to be the earliest effect of digitalis on transmembrane resting and action potential characteristics of normal Purkinje fibers The fact that ouabain under the conditions of this study caused prolongation of action potentials of Purkinje fibers in infarcted regions but not in normal regions indicates that the fibers in infarcted regions were more sensitive to this effect of the drug

Ouabain also caused an increase in conduction

twelfth edition Rotenberg G M ed Toronto 1978 Canadian Pharmaceutical Association pp 192 193
14 Rosen M R Wit A L and Hoffman B F Electrophysiology and pharmacology of cardiac arrhythmias IV Cardiac antiarrhythmic and toxic effects of digitalis Am Heart J 89 391 1975
15 Ferrier G R Digitalis arrhythmias role of oscillatory afterpotentials Progr Cardiovasc Dis 19 459 1977
16 Rosen M R Gelband H and Hoffman B F Correlation between effects of ouabain on the canine electrocardiogram and transmembrane potentials of isolated Purkinje fibers Circulation 47 65 19 3
17 Friedman P L Stewart J R Fenoglio J J Jr and Wit A L Survival of subendocardial Purkinje fibers following extensive myocardial infarction in dogs Circ Res 33 597 1973
18 Friedman P L Stewart J R and Wit A L Spontaneous and induced cardiac arrhythmias in subendocardial Purkinje fibers surviving extensive myocardial infarction in dogs Circ Res 33 612 1973
19 Lazzara R El Sherif N and Scherlag B J Electrophysiological properties of canine Purkinje cells in one day old myocardial infarction Circ Res 33 722 1973
20 Friedman P L Fenoglio J J Jr and Wit A L The time course for reversal of electrophysiological and ultrastructural abnormalities in subendocardial Purkinje fibers after extensive myocardial infarction in dogs Circ Res 36 127 1975
21 Allen J D Brennan F J and Wit A L Actions of lidocaine on transmembrane potentials of subendocardial Purkinje fibers surviving in canine infarcts Circ Res 43 4) 1978
22 Hondeghem L M Grant A O and Jensen R A Antiarrhythmic drug action selective depression of hypoxic cells, Am Heart J 87 602 1974
23 Hordof A J Edie R Malm J R Hoffman B F and Rosen M R Electrophysiologic properties and response to pharmacologic agents of fibers from diseased human atria Circulation 54 774 19 6
24 Rosen M R Danilo P Jr Alonso M B and Pippenger C F Effects of therapeutic concentrations of diphenylhydantoin on transmembrane potentials of normal and depressed Purkinje fibers J Pharmacol Exp Ther 197 594 1976
25 Brennan F J Cranefield P F and Wit A L Effects of lidocaine on slow response and depressed fast response action potentials of canine cardiac Purkinje fibers J Pharmacol Exp Ther 204 312 1978
26 Bigger J T Jr Bassett A L and Hoffman B F Electrophysiological effects of diphenylhydantoin on canine Purkinje fibers Circ Res 22 221 1968
27 Croxton F E Elementary Statistics with Application in Medicine New York 1953 Prentice Hall, Inc pp 209 244
28 Muller P Ouabain effects on cardiac contraction action potential and cellular potassium Circ Res 17 46 1965
29 Hoffman B F Effects of digitalis on electrical activity of cardiac fibers in Digitalis Fisch C Surawicz B ed, New York 1969 Grune & Stratton Inc pp 93-109
30 Leon J Ferrier G R and Moe G K The relationship of excitability to conduction in canine Purkinje tissue Circ Res 43 125 1978
31 Rosen M R Gelband H Merker C and Hoffman, B F Mechanisms of digitalis toxicity effects of ouabain on phase 4 of canine Purkinje fiber transmembrane potentials Circulation 47 681 1973
32 Wit A L and Bigger J T Jr Possible electrophysiological mechanisms for lethal arrhythmias accompanying myocardial ischemia and infarction Circulation 52 Suppl III 96 19 5
33 Kent K M Smith E R, Redwood D R and Epstein, S E Electrical stability of acutely ischemic myocardium Influences of heart rate and vagal stimulation Circulation 47 291 1973

Copyright information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner's consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients This consent is given on the condition however that the copier pay the stated per copy fee through the Copyright Clearance Center Inc 21 Congress Street Salem Mass 01970 617 744 3350 for copying beyond that permitted by Sections 107 or 108 of the U S Copyright Law This consent does not extend to other kinds of copying such as copying for general distribution for advertising or promotional purposes for creating new collective works or for resale

of ouabain to which the tissues were exposed in our experiments corresponds to that to which tissues are exposed in vivo when a therapeutic dose of a cardiac glyceride is administered In addition it is possible that other factors such as autonomic nervous system activity might modify the direct electrophysiological effects of digitalis in vivo For example digitalis is known to exert a strong indirect effect on the normal heart by increasing vagal tone [14] and enhanced vagal activity has been reported to inhibit ventricular arrhythmias in acute myocardial infarction Acetyl choline the chemical mediator of vagal effects has been reported to abolish digitalis induced oscillatory afterpotentials in certain types of cardiac tissue [15] It is also important to note that the possible indirect effects of ouabain on the electrophysiological properties of cardiac tissues due to its effects on myocardial oxygen consumption have not been assessed in the present study Finally since our results were obtained from tissue preparations made after infarction had been present for 24 hours they may have little relevance to arrhythmias occurring in the first few hours after myocardial infarction [3] Thus while the present study has shown that the abnormal subendocardial Purkinje fibers surviving in regions of acute myocardial infarction in dogs have enhanced susceptibility to the direct electrophysiological effects of ouabain much further study is required before the clinical significance of this observation can be ascertained

Summary

We compared the effects of ouabain 2 5 × 10 M on the electrophysiological properties of minimally depressed subendocardial Purkinje fibers surviving in regions of acute myocardial infarction with its effects on subendocardial Purkinje fibers in adjacent normal regions and in anatomically identical regions of noninfarcted hearts Experiments were carried out in vitro on left ventricular tissue preparations dissected from the hearts of dogs 24 hours after coronary artery ligation and from normal canine hearts Ouabain had no effect on maximum diastolic potential action potential upstroke or V_m of Purkinje fibers in normal or infarcted regions It prolonged the action potential duration in infarcted but not in normal regions In infarcted tissue preparations ouabain increased conduction velocity and failed to alter the effective and functional refractory periods while in normal tissue preparations the drug did not affect conduction velocity or the effective refractory period but caused an increase in the functional refractory period Ouabain did not cause spontaneous activity in normal tissue preparations In infarcted preparations it resulted in spontaneous activity in six of eight preparations studied This was due to the development of oscillatory afterpotentials in three preparations and phase 4 depolarization in one in the other two preparations the mechanism was uncertain Thus Purkinje fibers surviving in infarcted regions are more sensitive than normal fibers to the direct electrophysiological effects of digitalis

The authors wish to thank Evelyne Stefaniszyn for her technical assistance and Louise McCrady for the preparation of this manuscript

REFERENCES

1 Bellet S., Johnston C G and Schechter A The effects of cardiac infarction on the tolerance of dogs to digitalis, Arch Intern Med 54 509 1934
2 Travell J Gold G and Modell, W The effect of experimental cardiac infarction on response to digitalis, Arch Intern Med 61 184 1938
3 Morris J J Jr Taft C V Whalen R E and McIntosh H D Digitalis and experimental myocardial infarction Am Heart J 77 342 1969
4 Kumar R Hood W B Jr Joison J., Gilmour D P., Norman J C and Abelmann W H Experimental myocardial infarction VI Efficacy and toxicity of digitalis in acute and healing phase in intact conscious dogs J Clin Invest 49 358 1970
5 Selzer A. The use of digitalis in acute myocardial infarction Progr Cardiovasc Dis 10 518 1968
6 Karliner J S and Braunwald E Present status of digitalis treatment of acute myocardial infarction Circulation 45 891 1972
7 Dodek A Digitalis use in acute myocardial infarction current concepts Can Med. Assoc J 111 561 1974
8 Askey J M Digitalis in acute myocardial infarction J.A.M.A 146 1008 1951
9 Schenk K E Schuren K P., Buschmann H J Dennert J Meyer V Ramdohr B and Schroder R Rhythmusstorungen bei Digitalisbehandlung von Patienten mit akutem Myokardinfarkt Deutsch Med Wschr 96 663 1971
10 Lown B Klein M.D Barr I Hagemeijer F Kosowsky B D and Garrison H Sensitivity to digitalis drugs in acute myocardial infarction Am. J Cardiol 30 388 1972
11 Mason D T Zelis R Amsterdam E A and Massumi, R A Mechanisms of digitalis arrhythmias electrophysiologic and myocardial subcellular considerations *in* Cardiac Arrhythmias Dreifus L. S and Likoff W eds. New York, 1973 Grune & Stratton Inc., p 498
12 Braunwald E and Pool P E Pharmacologic treatment of cardiovascular disorders, *in* Harrison s Principles of Internal Medicine, eighth edition, Thorn, G W., Adams, R D., Braunwald E Isselbacher K J and Petersdorf R G eds New York 1977 McGraw Hill Book Company Inc., p 1209
13 Compendium of Pharmaceuticals and Specialties

Table I Clinical and ECG findings at rest

Athlete (initials & sport)	*Age*	*Heart rate*	*ECG feature*	*T inversion leads*	*ST anomalies*
1 B V soccer	20	60	LVH RVH	ILL	–
2 B P soccer	20	44	LVH	LPL, ILL	ERV
3 C A soccer	37	56	–	LPL, ILL	–
4 M M soccer	20	45	LVH RVH	RPL, ILL	–
5 M.A. canoeist	17	54	LVH	LPL	ERV
6 M.R. runner	18	55	–	ILL	–
7 R G rugby	18	70	LVH	RPL, ILL	ERV
8 S P basketball	18	63	LVH	LPL, ILL	–

Abbreviations LVH = left ventricular hypertrophy voltage criteria RVH = right ventricular hypertrophy voltage criteria RPL = right precordial leads LPL = left precordial leads ILL = inferior limb leads ERV = early repolarization variant.
mitral valve prolapse
spontaneous variability of T wa[illegible]

infused intravenously in each subject to increase the heart rate (HR) at least 30 beats/minute Infusion was adjusted to deliver 1 μg/mL of IS within 30 seconds Six athletes required a minimal dose of 5 μg to achieve the desired HR increase while two of them received 9 μg within 270 seconds None experienced any ventricular premature beats during IS infusion ECGs were recorded continuously up to third minute after the end of infusion and then at the fifth and tenth minute after infusion

Twenty minutes after the end of IS infusion when the ECG had indicated the return to control tracings atropine sulfate (AT) was administered intravenously in a single dose of 0 02 mg/kg of body weight within 30 seconds An AT test was performed in only seven of the eight subjects because one subject refused AT infusion The ECG was monitored continuously up to the third minute after the end of infusion and then at the fifth tenth fifteenth and twentieth minute after infusion

During pharmacological tests the VCG was recorded basally and when ECG tracings were made maximal effects of the drugs on the HR or T wave normalization were seen ECG tracings were accurately analyzed for T wave polarity and amplitude and for QT and QTc intervals[3]

Vectorcardiographic T loops in the frontal (FP) and horizontal planes (HP) were analyzed for (1) shape and sense of rotation (2) direction of maximum T vector ($\hat{V}max$ T) (3) QRS/T angle (A°QRST) and (4) length/width ratio (L/W)

Results

Resting ECG and VCG patterns *Resting ECGs of all athletes are shown in Fig 1 ECG features* are also summarized in Table I Four subjects had moderate and two others had marked sinus bradycardia

Four athletes fulfilled ECG voltage criteria of left ventricular hypertrophy (LVH) and two others had combined LVH and right ventricular hypertrophy (RVH)[illegible] Isolated T wave abnormalities were appreciable in five cases and were associated with the early repolarization variant (ERV)[illegible] in the remaining patients Two subjects had T wave inversion in the inferior limb leads (ILL) one in the left precordial (LPL) and the remaining patient in both limb and precordial leads

Case No 4 with MVP had a typical posteroinferior ischemia pattern[illegible] together with a distinct terminal T wave inversion in the right precordial leads (RPL) Case Nos 2 6 and 7 showed marked spontaneous variability of ECG tracings (see Fig 2) Resting QT and QTc interval were within normal limits in all cases

Resting VCG data are summarized in Table II

QRS/T angle in the frontal plane was abnormally wide in Cases 1 and 3 and in the horizontal plane in Cases 2 and 3 T loop rotation in the horizontal plane was counterclockwise (CCW) and the inscription of the efferent limb of the loop was slower than that of the afferent limb in all cases T loop shape in the horizontal plane showed a triangular pattern (see Figs 4 and 5) in four of six cases with negative T waves in the precordial leads and it was narrow in the remaining subjects In the three subjects with ERV[illegible] the ST vector oriented in the same direction as in the ECG tracings was appreciable Vectorcardiogram confirmed the left ventricular

T wave abnormalities in top ranking athletes effects of isoproterenol atropine and physical exercise

Paolo Zeppilli M D
Marco M Pirrami M D
Massimo Sassara M D
Riccardo Fenici M D
Rome Italy

Many authors have reported ST and T wave abnormalities as an unexpected finding in the electrocardiograms (ECGs) of top ranking athletes otherwise asymptomatic and fit for excellent performance Most of these authors agree about the benignity of these ECG anomalies especially when any evidence of organic heart disease is lacking[1, 3, 33, 39, 4, 4]
Recently[71] however we reported 12 cases of asymptomatic top level athletes with pseudoischemic T wave changes four of whom had asymptomatic mitral valve prolapse (MVP) and three who had an echocardiographic (ECHO) pattern of asymmetrical septal hypertrophy (ASH) Therefore the complete functionality of repolarization abnormalities in athletes is in our opinion at least questionable

In the present work a further eight top ranking athletes with repolarization abnormalities were investigated in order to ascertain

1 if ECG anomalies could account for any concealed organic heart disease

2 the mechanism underlying these ECG abnormalities in athletes

3 the diagnostic reliability of provocative tests with regard to these repolarization disorders

Materials and methods

Clinical and ECG data are summarized in Table I Eight top ranking athletes males aged between 17 and 37 years (mean 26 years) participating in different sports events particularly in the endurance type were referred to us by the Sports Medicine Institute of Rome (H Prof Venerando) for repolarization disorders Seven subjects were examined during their competitive season when they were well trained One subject (Case No 3) was examined 10 months after he had finished his competitive activity while he was still maintaining his physical fitness The follow up of this athlete continued for 12 years Another case (No 5) had a follow up period of 2 years All the subjects were completely asymptomatic Clinical examination and ECHO investigation were negative in seven of them One athlete (Case No 4) had auscultatory-echocardiographic features of mitral valve prolapse (MVP)[8] ECG tracings at rest and after pharmacological tests were made with a Hewlett Packard (HP) multichannel electrocardiograph Orthogonal Leads X Y Z and VCG loops were recorded with a HP vectorcardiograph (Moded 1507 A) using the Frank lead system

Resting ECGs and VCGs were taken 10 minutes after the athlete had been kept in the recumbent position ECG tracings were also recorded during and after rapid open hyperventilation (ROHV) Valsalva maneuver and standing

Subsequently a stress exercise ECG (EX) was performed in all athletes first by a 3 minute step test (Harvard) and then by bicycle ergometer maximal effort test On a second day after informed consent had been obtained a control ECG was recorded and thereafter a solution containing 1 μg/ml of isoproterenol (IS) was

Fr m the Institute f Med l P th logy Cath li Un ersity of th Sacred H art R m Ital

Rece ed fo publi tion M y 2 19 9
A pted fo p bl tio M y 28 19 9

Reprint requests Dr P olo Zepp lli Via Dieg S mo tti 54 00056 Lido d Ost a Roma It ly

000?-8703/80/080?13 + 10?01 00 0 1980 The C V Mosby Co

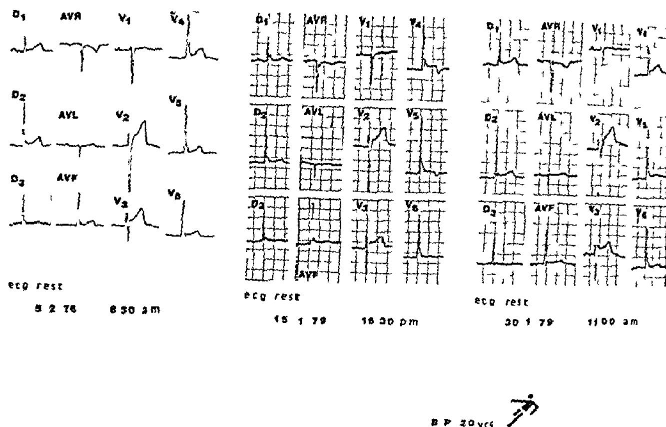


Fig 2 A 20 year old professional soccer player whose ECG tracings show marked spontaneous variability

Table II VCG findings at rest

Case	QRS loop	Frontal plane				Horizontal plane			
		V max T	A QRST	T loop shape and rotation	L/W	V max T	A QRST	T loop shape and rotation	L/W
1	LVH	−8	110	narrow ∞	—	12	42	wide CCW	1 4
2	LVH	3?	33	narrow CCW	3	65	120	narrow CCW	16
3	—	14?	100	wide CW	1 4	175	207	triangular CCW	—
4	LVH	[illegible]	43	narrow CCW	3	330	45	triangular CCW	—
5	—	15	27	wide CW	0 8	55	43	triangular CCW	—
6	—	5	45	narrow ∞	—	48	85	wide CCW	1 5
[illegible]	—	10	3?	narrow ∞	3	350	22	triangular CCW	—
8	—	30	15	narrow CW	5 8	37	?9	narrow CCW	6

Abbreviations LVH = left ventricular hypertrophy A QRST = QRS/T angle V max T = maximum T vector direction CW = clockwise CCW = counterclockwise ∞ = figure of eight L W = length/width ratio mitral valve prolapse

hypertrophy diagnosis in Cases No 1 2 and 4

Provocative tests and exercise ECG The ECG modifications induced by the Valsalva maneuver and ROHV were not the same in individual subjects (Table III) Standing worsened ECG abnormalities in six of eight cases (75%) Step test exercise normalized the ECG in six cases while maximal effort (Fig 2) reverted the T wave in all subjects (100% of cases) All athletes achieved maximal HR and O uptake (VO max) adequate to their physical fitness No subject exhibited pathologic ST changes or ventricular arrhythmias during and after effort

Pharmacological tests Isoproterenol completely reverted the T wave (see examples in Figs 3 4 and 5) in six cases (75%) and reduced T wave inversion in the remaining two T wave modification was observed coincident with a combined increase of HR and a decrease of absolute QT interval Average absolute QT interval at which T

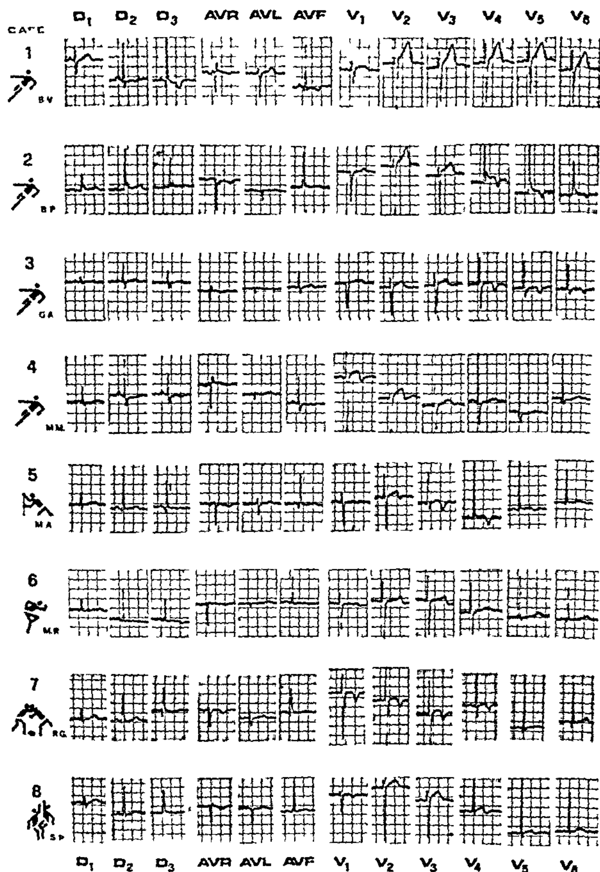
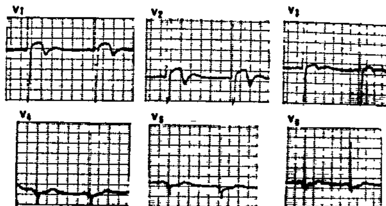
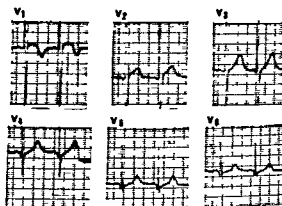


Fig 1 Resting ECG tracings



ISUPREL 8γ I.V.

AFTER 1





M.M. 18 yrs

Fig 4 An 18-year-old professional soccer player with MVP In this case also isoproterenol infusion reverted T wave abnormalities. H = VCG horizontal plane

even more intriguing because of its legal implications Many authors observed spontaneous [1-5, 3, 5, 6] or provoked [3, 30] idiopathic T wave abnormalities in normal untrained persons with a higher percent incidence in Negroes (maximum 33 9%) [5, 6, 61] than in Caucasians (average 0 5%) [1, 6, 3, 54]

Epidemiological ECG screening performed in an unselected white population of 12 000 sportsmen participating in different physical activities and belonging to various competitive levels evidenced a percent incidence of T wave abnormalities (0 5%) similar to that of untrained people With regard to selected highly trained groups the percent incidence of major repolarization disorders ranges between 4 1 and 18% [1, 0, 1, 33, 39, 3, 53, 61, 6] This supports the opinion that T wave abnormalities are more frequent in top level athletes especially when they practice an endurance activity This observation suggested the hypothesis that intensive training could play a role in the pathogenesis of such repolarization disorders

T wave abnormalities may be produced by central nervous system disease [3] In addition T wave and QT interval modifications have been experimentally induced either by unilateral stimulation or by removal of stellate ganglia [3, 6] or by brief or prolonged cardiac nerve stimulation or catecholamine infusion Moreover changes in T wave amplitude or polarity were obtained in dogs by isoproterenol infusion into different regions of ventricular myocardium [3] Daoud and co workers [6] emphasized that isoproterenol reverts more than 90% of primary T wave abnormalities not due to pericarditis or ischemia while it does not normalize secondary T wave changes

Neither atropine infusion nor atrial pacing were effective in normalizing T wave polarity [9] T wave normalization after isoproterenol therefore should not be related only to HR increase but to a combination of a critical increase of HR and

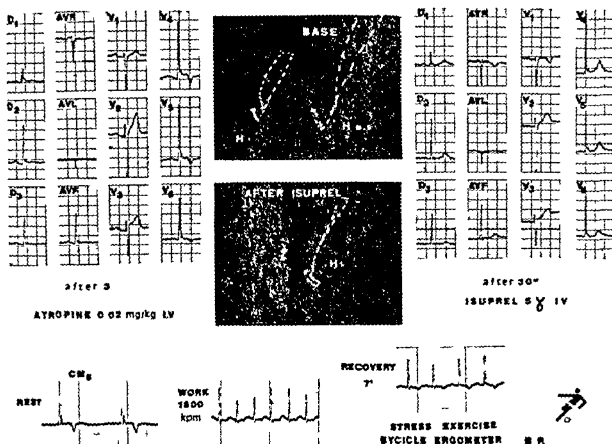


Fig 3 The same patient as shown in Fig Note complete normalization of T wave abnormalities after isoproterenol infusion and exercise H = VCG horizontal plane

Table III Effects of provocative tests exercise isoproterenol and atropine upon T wave abnormalities

Case	Valsalva	Hyperventilation	Standing	Exercise	Isoproterenol	Atropine
1	unchanged	unchanged	unchanged	normalized	normalized	unchanged
2	unchanged	reduced	worsened	normalized	normalized	unchanged
3	reduced	reduced	worsened	normalized	reduced	—
4	unchanged	reduced	worsened	normalized	normalized	unchanged
5	worsened	worsened	worsened	normalized	normalized	reduced
6	worsened	unchanged	unchanged	normalized	normalized	unchanged
7	normalized	worsened	worsened	normalized	reduced	worsened
8	reduced	reduced	worsened	normalized	normalized	unchanged

wave normalization had been observed was 0 34 ± 0 04 sec with an average HR of 90 1 ± 14 1 beats/minute

Despite a greater increase of HR (average 105 8 ± 8 82 beats/minute) and a similar QT interval shortening (average 0 34 ± 0 03 beats/minute) AT infusion did not significantly change T wave amplitude or polarity in five cases reduced T wave inversion in 1 case and worsened it in another case

Discussion

ST and T wave abnormalities simulating pericarditis or myocardial ischemia in asymptomatic subjects without clinical or instrumental evidence of cardiopathies have long since represented a cardiological puzzle Moreover when these anomalies are encountered in athletes otherwise suited for excellent cardiovascular performance and who participate in intensive training and exhaustive competitions the problem is

particularly in females[15 19 41 0 5] mostly with benign prognosis[1 8 9 10 17 3 49 7] even if cases of sudden death and myocardial infarction were reported Since MVP had been discovered also in asymptomatic excellent athletes[* 1] a new problem arose about the significance of this finding Therefore this study was conducted to assess the advisability of allowing physical activity in these subjects

A more detailed discussion on this argument is beyond the limits of this work but we think in agreement with Barlow s opinion[9 1] that an asymptomatic athlete with MVP should be allowed to take part in his sport activity provided that he did not experience ventricular tachyarrhythmias during effort

Notwithstanding this great volume of studies the pathogenesis and significance of ischemic ECG changes in MVP still remain substantially obscure In our previous experience[1] T wave abnormalities in top ranking athletes with an ECHO pattern of MVP had their abnormalities reverted by maximal effort in three out of four cases This behavior was also observed in a further four subjects (unpublished data)

An isoproterenol test has been performed only in the athlete with MVP included in this study (Fig 4) who achieved a complete normalization of the T wave pattern Although a large number of cases should be investigated to ascertain the reliability of the isoproterenol test in athletes with MVP and an ECG ischemic pattern we suggest that the presence of repolarization disorders in asymptomatic and arrhythmia free athletes with MVP must be considered with caution and requires a more detailed investigation only when exercise and isoproterenol test do not revert these abnormalities

Summary

Eight cases of top ranking athletes with repolarization disorders" are reported All subjects were asymptomatic and were otherwise suited for excellent cardiovascular performances Seven athletes did not show any evidence of heart disease Seven had MVP (mitral valve prolapse)

Umprompted variability of ECG tracings was observed in three cases Both isoproterenol infusion (IS) and maximal physical effort (EX) normalized T wave abnormalities in 100% of cases while atropine (AT) was ineffective despite an increase in heart rate greater than that caused by IS The authors emphasize the usefulness of a combined use of the EX and IS tests in ascertaining the clinical significance of T wave changes in healthy athletes

A neurogenic mechanism is proposed by the authors for the pathogenesis of these T wave abnormalities This hypothesis may explain the umprompted variability of ECG tracings and T wave normalization after maximal physical effort and isoproterenol infusion

We thank Professor A Venerando of the Sports Medicine Institute of Rome for his continuing encouragement and support of our studies and for his assistance in the functional evaluation of the athletes included in this study We are also grateful to Mr Madeddu Alessandro for his assistance in preparing the tables figures, and the manuscript

REFERENCES

1 Allen H., Harris, A and Leatham, A Significance and prognosis of an isolated late systolic murmur a 9- to 22 year follow up Br Heart J 36 525 1974
2 Abildskov J A., Adrenergic effects on the QT interval of the electrocardiogram AM HEART J 92 210 1976
3 Abildskov J A., Millar K Burgess, M J et al. The electrocardiogram and the central nervous system, Prog Cardiovasc Dis 12 212 1970
4 Autenrieth, G Surawicz, B., Kuo S and Arita, M. Primary T wave abnormalities caused by uniform and regional shortening of ventricular monophasic action potential in the dog Circulation 51 668 1975
5 Autenrieth, G., Surawicz B and Kuo S Sequence of repolarization on the ventricular surface in the dog AM HEART J 89 463 19 5
6 Baoder H.S Cardiovascular adaptations in the trained athlete in Lubich, T and Venerando A., eds. Sports Cardiology 1978 Bologna, 1980 Aulo Gaggi, pp 3-12.
7 Balsano F., Aguglia V and Salerno L Considerazioni patogenetiche sui cosiddetti quadri elettrocardiografici pseudoischemici " Boll. Soc Ital. Cardiol. 11 2, 1966
8 Barlow J B., and Pocock W A The problem of non-ejection systolic clicks and associated mitral systolic murmurs emphasis on the billowing mitral leaflet syndrome AM HEART J 90 636 19 5
9 Barlow J B., Bosman, C K Pocock W A and Marchand P Late systolic murmurs and non-ejection (mid late) systolic clicks AM HEART J 30 203 1968
10 Barlow J B Personal communication.
11 Bellettini, W and Pinelli, G Alterazioni primarie non patologiche della ripolarizzazione ventricolare Cardiol. Prat 20 35 1969
12 Beswick, F V and Jordan R C Cardiological observations at the 6th British Empire and Commonwealth Games, Br Heart J 23 116 1961
13 Biberman, L., Sarma, R., and Surawicz B T wave abnormalities during hyperventilation and isoproterenol infusion AM HEART J 81 166 1971
14 Boudoulas H., Wooley C., Reynolds J and Mazzaferri E. Mitral valve prolapse syndrome—evidence for a hyperadrenergic state (Abstr) Am J Cardiol 43 3?8 1979
15 Brown O R., Kloster F E., and De Mots H Incidence of mitral valve prolapse in the asymptomatic normal Circulation 51 and 52 (Suppl 2) 2 1975

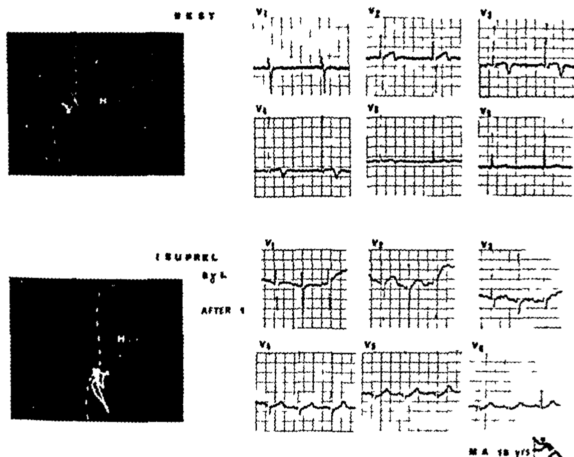


Fig 5 An 18-year-old canoeist (olympic rankin) The complete normalization of the T wave pattern after isoproterenol infu ion is clearly appreciable both on the ECG and on the VCG H = VCG horizontal plane

decrease of absolute QT interval duration caused by this drug Isoproterenol shortens monophasic action potential (MAP) duration due to the shortening of phase 2[31] This could explain the different effects of isoproterenol on normal and abnormal primary T wave changes In this regard we suggest that T wave abnormalities in top ranking athletes without clinical signs of organic heart disease if reverted by isoproterenol infusion or maximal physical effort should be considered functional We are in favor that such a diagnostic approach be routinely employed in these cases even if further investigation in a larger number of cases is required to define better the sensitivity and specificity of these tests

Pathogenesis of T wave abnormalities We have already suggested that primary T wave abnormalities in athletes could be neurogenic Prolonged physical training in fact is probably associated with both a decrease of resting vagal and sympathetic tone This could unmask in genetically predisposed athletes [5] a latent functional asymmetry of cardiac sympathetic nerves and induce inequality of ventricular repolarization resulting in T wave abnormalities[3] The normalization of ventricular repolarization obtained by both isoproterenol infusion and maximal effort could be explained as due to a uniform enhancement of sympathetic tone at high levels which overcomes functional asymmetry of resting cardiac sympathetic discharge

T wave abnormalities in MVP T wave abnormalities in subjects with MVP are a relatively common finding either as a typical posteroinferior ischemia" pattern or less frequently as diffuse T wave inversion [9, 33, 34, 35, 5] In addition patients with MVP have other ECG anomalies like atrioventricular conduction disturbances[5] and supraventricular and ventricular arrhythmias at rest and during effort [33, 37, 5, 49] Nevertheless MVP is a tremendously common finding in normal subjects

ita del quadro ECG di onda T labile pseusoichemica Boll Soc Ital Cardiol 20 9 1039 1975
55 Schwartz, P J., Verner R L. and Lown B Effects of stellectomy and vagotomy on ventricular refractoriness in dogs Circ Res 40 6 536 1977
56 Sloman G Wong M and Walker J Arrhythmias on exercise in patients with abnormalities of the posterior leaflet of the mitral valve AM HEART J 83 321 1972
57 Sloman G Stannard M Hare W S C Goble A J and Hunt D Prolapse of the posterior leaflet of the mitral valve Isr J Med Sci. 5 727 1969
58 Smith W G., Cullen K J., and Thorburn I O ECGs of marathon runners in 1962 Commonwealth Games Br Heart J 26 469 1964
59 Strauzenberg S E ECG repolarization changes in top athletes, a sign of myocardial lesion or an expression of specific adaptation? *in* Lubich, T., and Venerando A eds. Sports Cardiology 1978 Bologna 1980 Aulo Gaggi pp 415-432
60 Surawicz B The pathogenesis and clinical significance of primary T wave abnormalities *in* Advances in Electro cardiography New York, 1972 Grune & Stratton Inc.
61 Thomas, J., Harris, E and Lassiter G Observations on the T wave and ST segment changes in the precordial ECG of 320 young Negro adults Am J Cardiol 5 468 1960
62. Venerando A Frequence et signification des principales anomalies de l ECG chez l athlete Med. Hyg 26 1132 1968
63 Venerando A., Caselli G and Piovano G Anomalies of ventricular repolarization in athletes (a long term fol low up study) Med Sport 26 353 1973
64 *Venerando A., Masini, V., Rulli, V and Liberati* F Rilievi ECG su maratoneti e marciatori olimpici, Med Sport 2 908 1967
65 Venerando A and Rulli, V Frequency morphology and meaning of the ECG anomalies found in olympic marathon runners and walkers J Sports Med. Phys Fitness 4 135 1964
66 Venerando A Severini V., Piovano G and Coseu, M. Sulle anomalie delle fase di ripolarizzazione dell ECG dei giovani soggetti allenati, Boll. Soc Ital. Cardiol. 11 602 1966
67 Caselli G., Piovano G., and Venerando A A follow-up study of ventricular repolarization abnormalities in athletes *in* Lubich, T and Venerando A. eds. Sports Cardiology 1978 Bologna 1980 Aulo Gaggi pp 477 499
68 Wiener L. Rios, J C and Massumi, R. A. T wave inversion with elevated RS-T segment simulating myocardial injury AM HEART J 67 684 1964
69 Winkler A., Lopez M G Fitzgerald J W Goodman D J Schroeder J S and Harrison D C Arrhythmias in patients with mitral valve prolapse Circulation 52 3 1975
70 Yanowitz F Preston J B and Abildskov J A. Functional distribution of right and left stellate innervation to the ventricles production of neurogenic electrocardiographic changes by unilateral alteration of sympathetic tone Circ Res 18 416 1966
71 Zeppilli, P., Sandric S Caselli G Spataro A and Assorgi, G Comparative electrovectorcardiographic echocardiographic study in athletes with ST T wave abnormalities *in* Lubich T and Venerando A., ed., Sports Cardiology 1978 Bologna 1980 Aulo Gaggi, pp 735 748
72 Zoneraich S Rhee J J Zoneraich, O Jordan D and *Appel J Assessment of* cardiac function in marathon runners by graphic noninvasive techniques, Ann. N Y Acad Sci 301 900 1977

IMPORTANT
INFORMATION FOR AUTHORS

Effective June 1 1980 all manuscripts for the AMERICAN HEART JOURNAL should be sent to

Dean T Mason M D
Section of Cardiovascular Medicine
University of California
School of Medicine
Davis California 95616

16 Burgess M J Harumi K and Abildskov J A Application of a theoretic T wave model to experimentally induced T wave abnormalities. Circulation 34 660 1966
17 Chesler F Matisonn R E Lakier J B Pocock W A Obel I W P and Barlow J B Acute myocardial infarction with normal coronary arteries A possible manifestation of the billowing mitral leaflet syndrome Circulation 54 203 19 6
18 Chignon J C and Distel R Vectrocardiographic aspects of the abnormalities of the ventricular repolarization in high competition athletes Electrocardiology Advances in Cardiology Vol 16 55 1976 Basel S Karger
19 Cohen M Pocock W A Lakier J B McLaren M J Lachman A S and Barlow J B Four year follow up of black schoolchildren with non-ejection systolic click and mitral systolic murmurs AM HEART J 95 69 1978
20 Daoud F S Surawicz B and Gettes L S Effects of isoproterenol on the abnormal T wave Am J Cardiol 30 810 197..
21 De Maria, A N King J F Bogren H G Lies J E and Mason D T The variable spectrum of echocardiographic manifestation of the mitral valve prolapse syndrome Circulation 50 33 1974
22 De Maria A N *Amsterdam* E Vismara L A Markson W, Brocchini, R, and Mason D T The variable spectrum of rhythm disturbances in the mitral valve prolapse syndrome (Abstr) Circulation 49(Suppl 3) 2? 19/4
23 Ehlers H K Engle M A, Levin A R Grossman H and Fleming R. C Left ventricular abnormality with late mitral insufficiency and abnormal electrocardiogram Am J Cardiol 26 333 1970
24 Frank E An accurate clinically practical system for spatial vectorcardiography AM HEART J 70 365 1956
25 Giuliano G Sangiorgi M Pierangeli L Fragola P Nello S and Villanti, P Rilievi su un gruppo di pazienti protatori di un quadro elettrocardiografico di onde T labili pseudo ischemiche Boll Soc Ital Cardiol 20 1601 1975
26 Giuliano G Fragola P Caprna A Galante A Pierangeli L and Cannata D Anomalie aspecifiche della ripolarizzazione ventricolare Gior Ital Cardiol 8 968 19 8
27 Gooch A S Vicencio F Maranhao V and Goldberg H Arrhythmias and left ventricular asynergy in the prolapsing mitral leaflet syndrome Am J Cardiol 29 611 19 2
28 Grusin H Peculiarities of the African s electrocardiogram and the changes observed in serial studies Circulation 9 860 1954
29 Guazzi, M D Magrini F Olivari M T Polese A and Fiorentini C Influences of the adrenergic nervous system on the repolarization phase of the electrocardiogram Angiology 29 617 1978
30 Hanne Paparo N Wendkos M H and Brunner D T wave abnormalities in the electrocardiograms of top ranking athletes without demonstrable organic heart disease AM HEART J 81 743 1971
31 Hanne Paparo N Drory Y Schoenfeld Y Shapiro Y and Kellerman J Common ECG changes in athletes Cardiology 61 26 19 6
32 Hiss R G and Lamb L E Electrocardiographic findings in 122 043 individuals Circulation 25 947 1962
33 Hunt B P E Electrocardiographic tudy of 20 champion swimmers before and after 110 yard print swimming competition Can Med Assoc J 88 1251 1963
34 Jeresaty R M Etiology of the mitral valve prolapse-click syndrome Am J of Cardiology 36 110 1975
35 Jeresaty R M Mitral valve prolapse-click syndrome Progr Cardiovasc Dis 15 623 1973
36 Kambara H and Phillips J Long term evaluation of early repolarization syndrome (normal variant RS T segment elevation)
37 Kuo S and Surawicz B Relationship of transmembrane action potential form to the T wave and T loop *in* Vectorcardiography 3 Hoffman, I and Hamby R I, ed Amsterdam 1976 North Holland Publishing Company
38 Lepeschkin E, and Surawicz B The duration of the QT interval and its components in electrocardiograms of normal persons AM HEART J 46 9 1953
39 Lichtman J O Rourke A Klein, A and Karliner J Electrocardiogram of the athlete Arch. Intern Med. 132 763 1973
40 Littman D Persistence of juvenile pattern in the precordial leads of healthy adult Negroes with report of electrocardiographic survey on three hundred Negro and two hundred White subjects AM HEART J 32 370 1946
41 Markiewicz W Stoner J London E Hunt S A, and Popp R. L Mitral valve prolapse in one hundred presumably healthy females Circulation 51 and 52 (Suppl 2) 77 1975
42 Minamitani K Miyagawa M, Kondo M and Kitamura K The electrocardiogram of professional cyclists *in* Lubich, T and Venerando A, eds. Sports Cardiology 1978 Bologna 1980 Aulo Gaggi, pp 315-325
43 Nakamoto, K Electrocardiograms of 25 marathon runners before and after 100 meter dash. Jap Circ J 33 105 1969
44 New York Heart Association Criteria Committee Diseases of the Heart and Blood Vessels 7th ed., Boston 19 3 Little Brown & Company
45 Parisi A F Beckmann C H and Lancaster M C The spectrum of ST segment elevation in the electrocardiograms of healthy adult men J Electrocardiol. 4 2, 137 19 1
46 Piovano G Caselli G and Venerando A Cardiopathies observed in athletes, International Conference on Sports Cardiology Rome April, 1978 (In press)
47 Pipberger H V Computer diagnosis of the ECG and VCG *in* Vectorcardiography 3 Hoffman, I, and Hamby R. I eds Amsterdam 1976 North Holland Publishing Company
48 Pocock W A, and Barlow J B Post-exercise arrhythmias in the billowing posterior mitral leaflet syndrome AM HEART J 80 740 19 0
49 Pocock W A and Barlow J B Etiology and ECG features of the billowing posterior mitral leaflet syndrome Am J Med 51 731 1971
50 Procacci P M Savran S V Schreiter S L and Bryson A. L Prevalence of clinical mitral valve prolapse in 1 169 young women N Engl. J Med 294 1086 1976
51 Rizzon, P., Antonelli G Biasco G., Brindicci G., and Di Biase M Chronic juvenile A V nodal dysfunction associated with mitral valve prolapse Eur J Cardiol. 8/6 589 19 8
52 Rizzon P Biasco G Brindicci, G., and Mauro F Familial syndrome of mid-systolic click and late systolic murmur Br Heart J 35 245 1973
53 Rose K D Relationship of cardiac problems to athletic participation J.A.M.A 208 2319 1964
54 Sangiorgi M Giuliano G Tallanda, G., Marini, G P Villanti, P and Fragola, P Osservazioni sulla famigliar

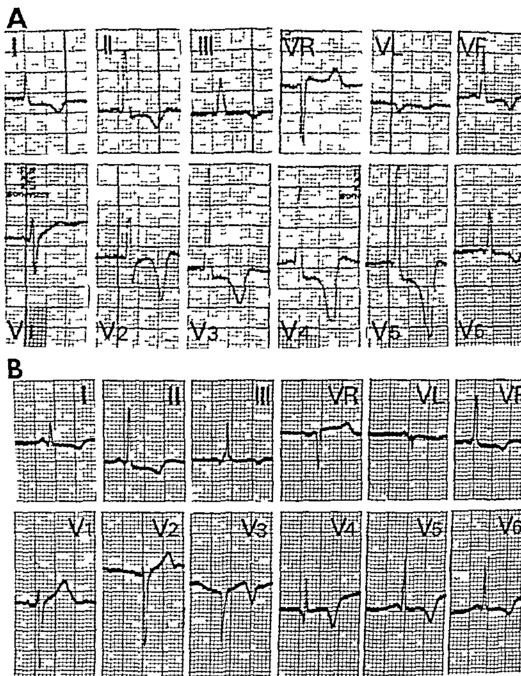


Fig 1 Pre *(A)* and postoperative *(B)* electrocardiograms Both tracings show a short PR interval (0 11 sec) New q waves (Leads V and V) are present after surgery

left ventricular angiogram was not different from that obtained preoperatively and selective coronary arteriography (Fig 3) revealed c mpl te release of the systolic obstruction of the LAD

Discussion

As far back as 1922 Crainicianu described for the first time the intramyocardial course of a segment of the left anterior descending coronary artery The frequency of this anomaly is relatively high as pointed out by Geiringer who found an incidence rate of 23% in his autopsy series Intramural segment occlusion is by far less common and it has been documented in about 0 5% of patients undergoing coronary arteriography

The ischemic nature of chest pain associated with significant systolic constriction of the LAD has been demonstrated in a group of subjects with milking effect and otherwise normal coronary arteries These patients showed myocardial lac

Case reports

Relief of angina by periarterial muscle resection of myocardial bridges

Amadeo Betriu M D
Julio Tubau M D
Gines Sanz M D
Jorge Magrina M D
Francisco Navarro Lopez M D F.A C C
Barcelona Spain

Systolic segmental narrowing of the left anterior descending coronary artery has been related to the presence of myocardial bridges Transient arterial constriction by muscle entrapment pro duces a characteristic milking effect which is easily recognized on angiography Patients with significant obstruction of the squeezed artery may develop ischemic chest pain It has been suggested that periarterial muscle resection to decompress the embedded vessel could be benefi cial in selected cases[1] Only five patients with this uncommon anomaly have been previously oper ated upon using such a technique but late follow up studies are lacking Two other cases have recently been reported in which arterial debridging was associated with revascularization procedures

This report documents a case of milking effect studied both before and 11 months after surgical repair of *two myocardial bridges* causing tran sient (systolic) occlusion of the left anterior de scending coronary artery

Case report

A 4 year-old man was admitted to the Hospital Clinico University of Barcelona in May 1976 for investigation of chest pain starting one year prior to admission Pain wa related to exertion and was relieved by nitroglycerin The patient was severely incapacitated (Class III NYHA) in spite of medical treatment with sedatives long acting nitrates and beta blocking agents Past history included typhoid fever (194) and two operations a gastrectomy (1943) and a chole cystectomy (1975) Cardiova cular examination revealed a soft S heart sound at the apex with no murmurs The heart rate was 60 beats per minute Blood pressure was 110/70 mm Hg Peripheral pulses were all palpable There were no signs of heart failure Chest x ray showed a normal sized heart The ECG (Fig 1) revealed sinus rhythm a short PR interval (0 11 sec) with notched QRS upstroke and no definite delta waves tall R waves (Leads V to V) and ST segment depres ion with deep inverted T waves in all leads Routine laboratory data were normal Transverse LV dimensions as well as wall motion and wall thickness were jud ed normal by echocardi ography An exercise test was discontinued because of chest pain and ST changes Double product at peak exercise was 1 760 mm Hg/minute (heart rate 110 beats per minute and systolic blood pressure was 160 mm Hg)

Combined right and retrograde left heart catheterization was carried out by the percutaneous technique No valvular or subvalvular pressure gradient was demostrated Left ventric ular end-diastolic pressure was moderately increased (24 mm Hg) Cardiac index was normal (3 L./min /M) A left ventric ular angiogram showed normal volumes and mass with an ejection fraction of 6 There was no mitral regurgitation Selective coronary angiography (Fig 2) demonstrated com plete systolic occlusion on two different segments of the LAD at its mid third The di tal vessel wa relatively narrow and short as it did not reach the apex The dominant ri ht coronary artery as well as the circunflex were entirely normal

Periarterial muscle resection was performed in June 1976 The mid third of the LAD was found to course close to the endocardium and its liberation resulted in right ventricular perforation. The defect was repaired and the postoperative course was uneventful despite the appearance of new q waves in Leads V and V (Fig 1) Since surgery the patient has remained asymptomatic of his chest pain A maximal exercise test performed in January 1977 was negative (double product 2 100 mm Hg/minute) A second hemodynamic study done 11 months after muscle resection showed normal LVEDP (10 mm Hg) and borderline cardiac index (2 5 L /min /M) The

From the Dep rtment of Medi i D is o of Card ology Hospital Clini o Un v rsty f B elona S h l of Medicine B rc l na Spain.

Recei ed fo publi tion Sept 11 19 8
Accepted f r publ cati n Jan 4 1979

Reprint requests D Amadeo B tri Di isi n of C rd l gy Hosp tal Clini o Casano a 147 Bar l 11 Spain

000 -8703/80/080 23 + 04$00 40 0 1980 The C V Mosby Co

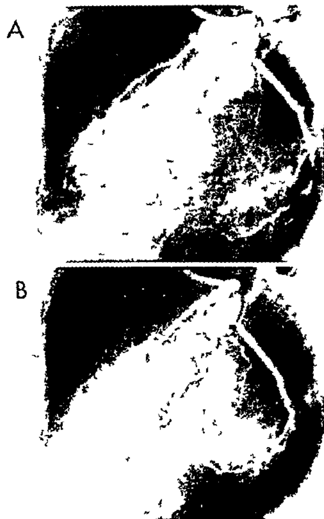


Fig 3 Diastolic *(A)* and systolic *(B)* frames showing release of obstruction following periarterial muscle resection

terial debridging and aortocoronary bypass grafting are probably not required in most patients with mural coronaries when arterial entrapment is not associated with fixed obstructions The lack of success of unnecessary combined procedures may be due to hemodynamic burden derived from flow competition

Summary

A 47 year old man presented with exertional angina Selective coronary arteriography showed complete systolic segmental occlusion of the left anterior descending coronary artery producing milking effect Permanent relief of symptoms was achieved by surgical excision of myocardial bridges Postoperative angiography performed 11 months later was normal Periarterial muscle resection should be considered in symptomatic patients with this rare anomaly

REFERENCES

1 Bourassa M G Noble J Dyrda I and Petitclerc R Myocardial bridges and milking effect of the left anterior descending coronary artery normal variant or obstruction? Circulation 51 and 52 (Suppl II) 35 1975
2 Binet J P Piot C Planche C, Leriche H Raza A Bourdil M and Kone A Pont myocardique comprimant l artere interventriculaire anterieure Arch Mal Coeur 68 87 1975
3 Slany U A Mosslacher H and Wolner E Myokardbrucke Ursache einer herzphasenabhangigen Koronarstenose Deutsche Med Wschr 101 653 19 6
4 Noble J Grondin P and Bourassa M G Successful periarterial muscle resection for myocardial bridging and milking effect of the left anterior coronary artery (Abstr) Am J Cardiol 39 267 1977
5 Faruqui A M Maloy W Felner J M Schlant R C Logan W D and Symbas P Symptomatic myocardial bridging of coronary artery Am J Cardiol 41 1305 1978
6 Crainicianu A Anatomische Studien uber Die Koronararterien und externmentelle Untersuchungen uber ihre Durchangigkeit Virchows Arch Pathol Anat 238 1 1922
7 Geiringer E The mural coronary Am Heart J 41.358 1951
8 Noble J Bourassa, M G Petitclerc R and Dyrda I Myocardial bridging and milking effect of the left anterior descending coronary artery normal variant or obstruction? Am J Cardiol 37 993 1976
9 Pichard A D Meller J Teichholz L E Lipnik S Gorlin R and Herman M V Septal perforator compression (narrowing) in idiopathic hypertrophic subaortic stenosis Am J Cardiol 40 310 1977
10 Brewer A L Bilbro R H and Bartel A G Myocardial infarction as a complication of coronary bypass surgery Circulation 47 58 1973
11 Sternberg L Wisneski J A Ullyot D J and Gertz E W Significance of new q waves after aortocoronary bypass surgery Correlation with changes in ventricular wall motion Circulation 52 1037 1975
12 Gambetta M and Childers R W Rate-dependent right precordial Q waves Septal focal block Am J Cardiol 32 196 1973
13 Polacek P Relation of myocardial brid es and loops on the coronary arteries to coronary occlusions Am Heart J 61 44 1961
14 Edwards J C Burnsides C Swarm R L and Lansing A I Arteriosclerosis in the intramural and extramural portions of coronary arteries in the human heart Circulation 13 235 1956

tate production and ST segment depression on the ECG during atrial pacing Thus ischemia seems to be triggered by a critical shortening of the diastolic filling period that compromises local O delivery

The intramural location of the LAD in the embryo points toward a congenital origin of this anomaly Although the delayed appearance of symptoms remains unclear it has been postulated that the acquisition of the milking effect could be secondary to progressive muscle growth and hypertrophy[5] Four out of 11 patients studied by Noble and associates had left ventricular hypertrophy and one of them was found to have a mild muscular subaortic stenosis Septal perforator compression has recently been documented in subjects with idiopatic hypertrophic subaortic stenosis[8] Slany and co workers reported a case in which histologic examination of excised muscle showed a marked thickening of fibers The finding of tall R waves in our case is in keeping with the diagnosis of hypertrophy but analysis of the angiograms revealed a normal left ventricular mass In addition echocardiographic assessment of both septal and posterior wall thickness was also normal Interestingly enough the LVEDP became normal after surgery and its dramatic reduction suggests in spite of a moderate fall in stroke volume an improvement in left ventricular compliance Reversal of ischemia suggested by decreased ST segment depression after surgery provides a satisfactory explanation for this finding

The presence of new q waves deserves comments Their appearance following revascularization procedures has been related to the occurrence of a myocardial infarction at the time of surgery an hypothesis substantiated by the finding of LV wall motion abnormalities in corresponding segments Since the second angiogram was unchanged infarction is unlikely Absence of infarction is also suggested by the regression of a previously elevated LVEDP On the other hand the LAD was not opened or hurt during the operation and it was found to be patent afterwards A logical explanation for the appearance of new precordial q waves is provided by the development of a septal focal block this form of segmental conduction disturbance being a consequence of the full thickness myotomy Pre excitation does not seem to account for the presence of new q waves as they were confined to Leads V_3



Fig 2 Preoperative left coronary angiograms (lateral view) in diastole *(A)* and systole *(B)* Note that the LAD becomes occluded *(arrows)* in systole

and V while the remaining leads did not show AV conduction changes In addition ajmaline administration failed to modify the atrioventricular conduction pattern

Prognosis of this anomaly is unknown Unexpected sudden death attributed to myocardial bridges has never been confirmed Disagreement exists in regard to their relationship with coronary atherosclerosis[7, 3] If one accepts that they play a role in the genesis of atheroma excision of bridges would undoubtedly be beneficial Release of obstruction may result in permanent relief of symptoms as demonstrated in our patient who remains free of angina 27 months after surgery Therefore it seems reasonable to recommend corrective surgery in disabled patients with significant systolic arterial constriction due to myocardial bridges Combined periar



Fig 1 High power magnification of an area of skeletal muscle showing infiltration by eosinophilic granular cells with areas of focal necrosis and nuclear anaplasia

Shortly after admission right ventricular pacemaking was established but the pacer failed to capture at times due to perforation into the pericardial cavity A permanent epicardial pacemaker was placed via a left anterior thoracotomy At thoracotomy numerous greyish nodules were found throughout the myocardium the pericardium the lungs and the pleura Four hundred milliliters of bloody pericardial fluid were drained

Biopsies of the myocardium pericardium lung and pleura were obtained Histological examination of the myocardial specimen revealed complete replacement of the myocardial tissue by granular cell tumor histologically similar to that obtained from the previous axillary and subcutaneous shoulder lesion Again no increase in mitotic activity was noted There was some nuclear anisocytosis but no anaplasia or necrosis The lung specimen showed a subpleural nodule extending into the pulmonary parenchyma composed of well differentiated granular cells

The patient was discharged from hospital 14 days later with good pacemaker function and was maintained on digitalis and diuretics until her death four months after discharge Autopsy permission was refused

Discussion

GCM is considered to be a rare tumor of soft tissue Nevertheless many cases were reported

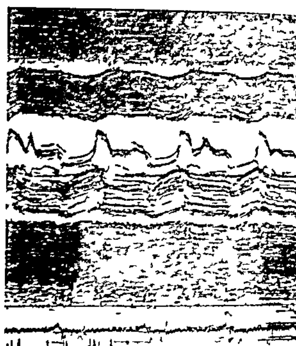


Fig 2 The echocardiogram shows marked thickening of the interventricular septum and the posterior left ventricular wall with diminution in the diameter of the left ventricular cavity There is a small posterior pericardial effusion

since 1926 when Abrikossof[3] described in detail the features of the tumor The term myoblastoma was questioned by some and many other terms have been proposed No agreement exists regarding the tumor s biological nature and origins Derivation from precursors of voluntary muscle cells viral factors response to parasitic infection perineural degeneration metabolic alterations lipoid thesaurismosis degeneration of the muscle fibers and derivation from Schwann cells have been suggested [4]

GCM is most frequently found in oropharyngeal and subcutaneous tissue but its occurence in a wide variety of sites has been well documented [1] It may occur in the eyelid breast colon ovaries or bronchus

It is believed that the tumor is generally nonmalignant and rarely metastasizing [6,11] although accounts of malignant forms have been reported [13,16] The tumor appears to be more frequent in women and blacks with a higher incidence in the third and fourth decades [1]

Strong and colleagues et al[1] reported three malignant lesions in their series of 95 cases one of which was cured by re excision Their statement that tumor size rapidity of growth, and invasion of adjacent structures may be more significant features in differentiation of benign from malig

Malignant granular cell myoblastoma with metastatic cardiac involvement: Case report and echocardiogram

George Kubac, M.D., F.R.C.P.(C)
Ian Doris, M.B., Ch.B., M.R.C.P. (U.K.), F.R.C.P. (C)
Milena Ondro, M.D.
Peter W. Davey, M.D., F.R.C.P.(C)
Edmonton, Alberta, Canada

Granular cell myoblastoma (GCM) is a rare soft tissue tumor of which the vast majority are benign. Our case concerns a malignant variety which presented clinically as heart block.

The echocardiographic findings are described together with the histological findings in the primary tumor and the metastatically infiltrated myocardium.

Case report

The patient was a Caucasian female who was 43 years old at the time of the final admission.

Two years previously she had had a mass excised from the left deltoid muscle. The pathological specimen was a 7 by 5 by 4.2 cm mass consisting of firm grey brown tissue with admixed gritty white areas. The tumor was composed histologically of regular cuboidal cells with granular eosinophilic cytoplasm and small central nuclei. Most of the specimen was organized into small packages separated by connective tissue septae, but in one area there was focal necrosis with the adjacent cells showing some anaplasia. Included in this zone were a few atypical mitotic forms. In view of the paucity of mitotic activity, the diagnosis of a benign granular cell myoblastoma was made.

Approximately one year later the mass recurred with axillary lymphadenopathy. Repeat biopsy (Fig. 1) was performed. The specimen showed infiltration of the muscle by large masses of eosinophilic granular cells with focal areas of nuclear anaplasia and gigantism. In view of the course of the disease, the diagnosis was changed to malignant granular cell myoblastoma in spite of the persistent relative paucity of mitotic activity and cellular pleomorphism. Further investigations in search of metastatic disease were carried out including mammography, lung scan, liver and spleen scan, and bone marrow biopsy which were all normal.

Radiographs of the lumbar vertebrae showed sclerotic changes and the isotope bone scan showed widespread metastases in the pelvis, ribs, and spine.

On the final admission the patient was pale and thin on examination. Blood pressure was 90/[illegible]0. The heart rate was 25/minute. Jugular venous pressure was 12 cm H_2O and a left ventricular gallop was heard. The liver was smooth, soft, and slightly enlarged. No evidence of lymphatic enlargement was found.

The chest x-ray showed cardiomegaly with pulmonary hilar congestion. The CBC was normal. SGOT, LDH, and alkaline phosphatase were moderately elevated. The protein and immunoelectrophoresis were normal. ECG showed A-V block of third degree with effective heart rate of 28 per minute and an atrial rate of 80 per minute. Later, while monitoring the patient, long episodes of asystole (the longest 6 seconds) were demonstrated. Occasionally the patient was in sinus rhythm with a right bundle branch block and left anterior hemiblock. Complete left bundle branch block was transiently present on the ECG.

Echocardiography (Fig. 2). Standard M mode echocardiography was performed using commercially available equipment. Recordings were made with a 3.5 MHz transducer and recorded with a Honeywell strip chart recorder CRT Visicorder 1858.

The echocardiogram showed marked symmetrical thickening of the interventricular septum ([illegible] mm) and the posterior wall of the left ventricle (20 mm). No systolic change in thickness of the interventricular septum and only 2 mm further thickening of the posterior left ventricular wall occurred.

The left ventricular cavity was reduced on size with diastolic and systolic diameters of 34 mm and 30 mm., respectively. There was dilatation of the left atrium (15 mm). The EF slope of the anterior leaflet of the mitral valve was decreased (62 mm/sec.) A small posterior pericardial effusion was present. Based on these findings a diagnosis of infiltrative cardiomyopathy was made.

From the Departments of Medicine, Radiological Sciences, and Laboratory Medicine, Royal Alexandra Hospital, Edmonton, Alberta, Canada.

Received for publication June 1[illegible], 1979.

Accepted for publication Aug. 6, 1979.

Reprint requests: George Kubac, M.D., No. [illegible]31 Royal Alexandra Place, 10106-111 Avenue, Edmonton, Alberta, Canada T5G 0B4.

Present address: Dept. of Radiology, Henderson General Hospital, Hamilton, Ontario, Canada.

0002-8703/80/080227 + 03$00.30/0 © 1980 The C. V. Mosby Co.

Clinical pathologic conference

Infarct expansion: The "second event" after acute myocardial infarction

Kenneth J. Silverman, M.D.
Grover M. Hutchins, M.D.
Baltimore, Md.

Clinical course

This 57-year-old male was in excellent health until one day prior to admission when he first noted substernal chest pain like indigestion. He presented to the emergency room after the pain persisted for two hours. An electrocardiogram was normal (Fig. 1) and he was sent home. Thirty-six hours later he returned to the emergency room because of unremitting chest pain of increasing severity. The electrocardiogram demonstrated changes of an acute anterior myocardial infarction (Fig. 2) and he was admitted.

The past medical history was remarkable for excellent health. He had no previous cardiorespiratory symptoms and took no medications. His cardiac risk factors included a 70 pack-year smoking history and a positive family history with a brother succumbing to a myocardial infarction at age 55.

The blood pressure was 90/60 mm Hg, pulse rate 70 per minute and regular, respiratory rate 14 per minute. There was no jugular venous distention. Basilar rales were audible in both lung fields. The precordium was quiet with no palpable heaves. The point of maximal impulse was in the fifth left intercostal space in the mid-clavicular line. The first and second heart sounds were normal. No murmurs were heard but an S gallop was present. No hepatosplenomegaly or peripheral edema was present. The admission chest radiograph revealed bilateral interstitial infiltrates and minimal cardiomegaly. The admission electrocardiogram demonstrated changes of an acute anterior myocardial infarction with prominent ST segment elevation in Leads I, aV_L, and V through V_5 and ST segment depression in the inferior leads. New Q waves were present in Leads V_2 and V_3 that were not present in the previous day's electrocardiogram.

The chest pain was relieved with 3 mg of intravenous morphine sulfate. After an initial diuresis with a total of 60 mg of intravenous furosemide, he did well with no dyspnea, no further chest pain, no arrhythmias, good urine output, and a stable blood pressure of 110/70 mm Hg. The peak CK value was 850 I.U./L. This was obtained on admission with declining serial values over the first 24 hours of admission. The electrocardiogram evolved Q waves in Leads V_1 through V_5, persistent 2 to 3 mm ST segment elevation in Leads V through V_4 and lesser elevation in Leads I, aV_L, and V. There was minimal ST depression in the inferior leads. He did well until six days after admission when he complained of chest pain and shortness of breath. Physical examination revealed a blood pressure of 85/60 mm Hg and rales to the infrascapular border bilaterally. No rubs and no new murmurs were audible. An S gallop was present but no abnormal precordial pulsations were noted. The chest radiograph demonstrated a prominent bilateral perihilar alveolar and interstitial infiltrate and minimal increase in the cardiac silhouette from admission. The electrocardiogram demonstrated the evolution of an anterior myocardial infarction as well as acute ischemic changes with further ST segment elevation in Leads I, aV_L, and V through V and further depression in the inferior leads than was present on tracings taken since admission (Fig. 3). Serial CK values obtained at 4 hour intervals over the

From the Cardiovascular Division of the Department of Medicine and the Department of Pathology of The Johns Hopkins Medical Institutions, Baltimore, Md.

Supported by grant [illegible] from the National Institutes of Health, Public Health Service, Department of Health, Education and Welfare.

Received for publication [illegible]

Reprint requests: Dr. Grover M. Hutchins, Department of Pathology, The Johns Hopkins Hospital, Baltimore, Md. [illegible]

0002-8703/80/080230 + 09$00.90/0 © 1980 The C. V. Mosby Co.

nant types would seem to be borne out by our case

Moscovic and Azar[18] observed that in one third of the cases the onset of a second or multiple tumors was preceded by surgical or therapeutical manipulation of the primary lesion

Radiation therapy was generally disappointing[13] [?] but Hunter and Dewar[7] give it some merit and describe survival times two or three times longer in treated than in untreated patients

To our knowledge the role of chemotherapy has not yet been established

Primary cardiac involvement by GCM was reported by Roth and Spain in 1952 in a patient with congestive cardiac failure The tumor involved pericardial and myocardial tissues at the left atrial level above the atrioventricular sulcus

Disseminating metastasizing GCM with multisystem involvement including pericardium and myocardium was reported by Svejda and Horn and by Khanholkar[13] Our case is to our knowledge the third reported case of metastasizing GCM with cardiac involvement Our patient was a middle aged woman who twice had surgical intervention and had a primary muscular tumor A one year history of mild shortness of breath did not alarm her and it was the syncopal attack that brought her to a cardiologist s attention Complete A V block and episodes of asystole were the most dramatic events The echocardiogram with thickened ventricular walls and reduced interventricular septal and posterior left ventricular wall motion showed changes characteristic of infiltrative myopathy Associated were increased left atrial diameter and the presence of a pericardial effusion The causes of symmetrical septal hypertrophy such as left ventricular pressure overload were not present The patient s history together with the radiographic and isotope findings in the spine suggested metastatic disease The echogenic features could not be distinguished from the other causes of infiltrative cardiomyopathy

Morbid anatomical features strongly resemble the case of Khanolkar with the myocardium being sprinkled with numerous tumor nodules

Despite the extensive involvement by tumor the patient managed to survive the acute situation with A V block and she lived with a pacemaker for four months after her discharge from the hospital

Summary

A malignant form of granular cell myoblastoma originating in the shoulder gave rise to metastatic cardiac involvement causing infiltrative cardiomyopathy with heart block The patient survived four months with a permanent pacemaker The echocardiographic and histological features are described and the literature is reviewed Features shown on the echocardiogram are indistinguishable from other causes of infiltrative cardiomyopathies

REFERENCES

1 Abrikosof F A Uber myome ausgehend von der quer gestreiften willkurlichen Muskulatur Virchows Arch Patol Anat 260 215 192[?]
2 Willis R A Pathology of Tumours 4th ed London 1967 Butterworths pp 761 763
3 Walter J B and Israel M S General Pathology 4th ed London 19 4 Churchill Livingstone p 301
4 Geschickter C F Tumors of muscle Am J Cancer 22 378 1934
5 Fisher E R and Wechsler H Granular cell myoblastoma a misnomer Am J Cancer 15 936 1962
6 Vance S F and Page Hudson R Granular cell myoblastoma Am J Clin Pathol 52 208 1969
7 Hunter D T and Dewar J P Malignant granular cell myoblastoma Am J Surg 26 554 1960
8 Oparah S S and Subramanian V A Granular cell myoblastoma of the bronchus Ann Thorac Surg 22 1.9 19 6
9 Rubenzik R and Tenzel R R Granular cell myoblastoma of the lid Ann Opht 8 471 1976
10 Weitzner S Lockard V G and Nascimento A G Granular cell myoblastoma of the cecum Dis Colon Rectum 19 675 1976
11 Holland J F and Frei E Cancer Medicine Philadelphia 1959 1973 Lea & Febiger
12 Pack, G T and Ariel I M Tumors of the Soft Somatic Tissues New York 1958 Paul B Hoeber Inc. p 541
13 Khanolkar V R Granular cell myoblastoma Am J Pathol. 23 721 1947
14 Ross R C Miller T R and Foote F W Malignant granular cell myoblastoma Am J Cancer 6 112 1952
15 Crawford E S and De Bakey M E Granular-cell myoblastoma Am J Cancer 6 786 1953
16 Svejda J., and Horn V Disseminated granular-cell pseudotumour so-called metastasising granular cell myoblastoma J Pathol Bact 76 343 1958
17 Strong E L McDivitt R W and Brasfield R D Granular cell myoblastoma Cancer XXV 415 19 0
18 Moscovic E A., and Azar H A Multiple granular cell tumours ("myoblastomas") Am J Cancer 20 2032 1967
19 Roth D and Spain D M Granular-cell myoblastoma of the myocardium Am. J Cancer 5 302, 19 2
20 Abbasi A S Ellis, N., and Child J Echocardiographic features of infiltrative cardiomyopathy (Abstract) J Clin. Ultrasound 2 221 1974
21 Borer J S and Henry W Echocardiographic observations in patients with systemic infiltrative disease involving the heart Am J Cardiol 39 184 1977
22 Assad Morell, J L Jajik A. J and Giuliani, E R Echocardiographic analysis of the ventricular septum Progr Cardiovasc Dis 17 219 19 4

next 24 hours remained within normal limits He was treated with intravenous morphine sulfate and furosemide with resolution of his symptoms and return of the ST segments to their position prior to this episode with persistent precordial elevation The next day he had another episode of chest pain and shortness of breath There were no associated ECG changes or CK elevation The chest pain was quickly relieved with morphine sulfate but despite furosemide and digoxin he continued to have slight shortness of breath and evidence of persistent pulmonary congestion on physical examination and chest radiograph After another episode of chest discomfort he was placed on nitroglycerin ointment which was well tolerated He had no further chest discomfort However 21 days after admission he unexpectedly developed ventricular tachycardia Despite repeated attempts at electrical cardioversion and extensive resuscitation efforts he was unable to maintain a pulse or blood pressure

Clinical discussion

DR KENNETH J SILVERMAN This case raises the common problem of a patient with a stable presentation and initially uneventful course following an acute myocardial infarction who rapidly and unexpectedly deteriorates with further chest pain or heart failure To maximize the patient s chance of survival the etiology of the patient s deterioration must be established quickly with a minimum of risk Extension of the myocardial infarction ventricular septal rupture ventricular free wall rupture papillary muscle rupture or dysfunction ventricular aneurysm formation pericarditis and pulmonary embolism are complications that must be carefully considered

Recurrence of chest pain onset of heart failure re evolution of ST segments and re evolution of CK are clues to myocardial infarct extension A study utilizing serial precordial ST segment mapping and serial CK values demonstrated evidence of infarct extension in greater than 50% of acute transmural anterior myocardial infarctions at an average of 5 8 days after admission The extension of myocardial injury may seriously compromise cardiac function and is a major determinant of mortality

Ventricular septal rupture complicates from 1% to 2% of all myocardial infarctions The infarct is usually transmural and the rupture usually occurs within the first week The presentation is often an abrupt deterioration in clinical status, with left ventricular failure a new pansystolic thrill and a loud pansystolic murmur [4] There may be further chest pain at this time Although the prognosis is poor death is often not sudden permitting time for diagnosis and treatment

Rupture of the free wall of the ventricle is a rare but catastrophic event with an average incidence of approximately 7% in autopsy series of patients with acute myocardial infarctions[5] Rupture is more common in patients suffering their first transmural infarction and may involve the anterior wall more frequently The most common presentation is sudden death usually within the first week after infarction [6] There are no characteristic features of the examination after rupture although findings consistent with cardiac tamponade may be present if there was slow leakage of blood and a blood pressure was maintained Sudden increase in amplitude of the T wave or reversal of previously inverted T waves has been described as a clue to the possibility of acute hemopericardium Some patients may experience repeated and prolonged chest pain which may be an indication of impending rupture with slow leakage of blood into the pericardium [7, 8]

Papillary muscle rupture has been noted at autopsy in as many as 5% of acute myocardial infarctions [9] It is not related to the size of the infarction most frequently occurring in infarctions that are relatively small in size and posterior in location The presentation is similar to ventricular septal rupture with dramatic deterioration in the patient s condition most frequently within the first week occasionally associated with chest pain [4] There is evidence of left ventricular failure and usually a loud pansystolic murmur but a prominent thrill is unusual Like ventricular septal rupture death is not sudden permitting time for diagnosis and treatment

Differentiating between ventricular septal rupture and papillary muscle rupture in a patient with sudden deterioration and a new systolic murmur can be difficult and may require insertion of a flow directed balloon catheter An increase in the oxygen saturation on passing from the right atrium to the right ventricle is evidence of a ventricular septal defect while prominent regurgitant V waves on the pulmonary capillary wedge tracing is evidence of mitral regurgita

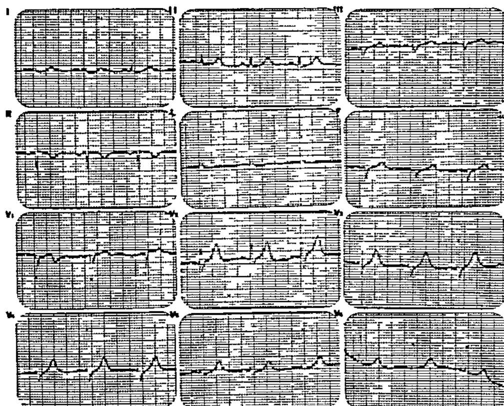


Fig 1 Initial 12 lead electrocardiogram is within limits with no acute ischemic changes

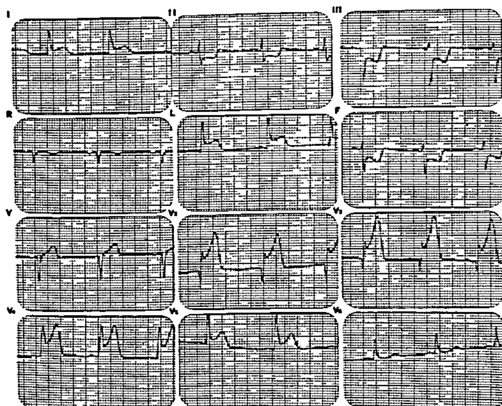


Fig 2 ECG taken on admission reveals changes of an acute anterior myocardial infarction

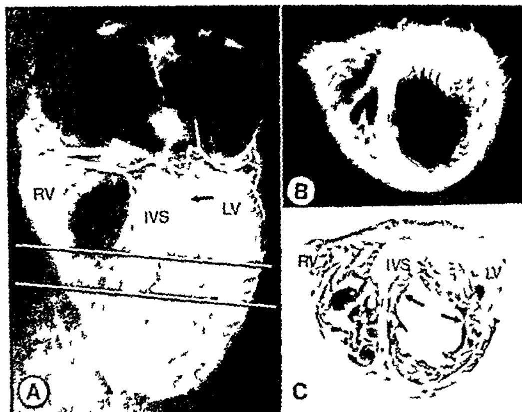


Fig 4 A through C A Postmortem coronary arteriogram The left anterior descending coronary artery is severely narrowed in its proximal portion (arrow) and its distal reaches are poorly filled. The apical region of the left ventricle is expanded B Radiograph of transverse section of the heart at the level shown by lines in A The infarcted anterior septal wall is markedly thinned compared to the surviving inferior lateral wall. C Cross photograph of the same heart section shown in B The infarct margins are at the arrows The expansion of the infarct is shown by the lateral displacement of the anterior papillary muscle complex

ing a transmural myocardial infarction Inspiration or motion often intensify the pain which is often exacerbated by lying flat and relieved by sitting up Splinting and dyspnea occasionally associated with pericarditis may be misdiagnosed as increasing congestive heart failure On auscultation a typical three component rub is often present but occasionally the rub may be heard only in systole or diastole and is misdiagnosed as a systolic or diastolic murmur or no rub is heard Low grade fever is usually present The chest radiograph may demonstrate an enlarging cardiac silhouette due to a pericardial effusion The electrocardiogram may have characteristic ST segment elevation but this is often not present Pericardial inflammation may predispose to arrhythmias

Non-cardiac causes of chest pain or hemodynamic deterioration must always be considered Pulmonary emboli may present with chest pain dyspnea increasing heart failure fever and tachycardia The chest pain of a dissecting aortic aneurysm is often localized in the posterior thorax but can present with anterior chest pain A murmur of aortic insufficiency and a widened mediastinum are useful clues Acute abdominal conditions must not be overlooked as an etiology of chest pain

Our patient's presentation emphasizes the importance of a careful history in the initial evaluation of a patient with chest pain The physical exam electrocardiogram and CK all may be normal Our patient suffered a large anterior transmural myocardial infarction The CK value probably peaked in the 36 hour interval between his initial emergency room visit and admission with the admission value of 800 IU/L on the descending portion of the CK curve

This patient did well until the sixth hospital day when he developed chest pain associated with pulmonary congestion a fall in his blood pressure and prominent electrocardiographic changes No

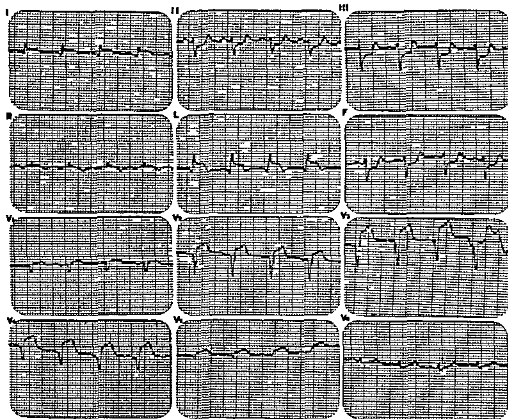


Fig. 3. ECG taken during pain on day 6 reveals evolution of anterior transmural myocardial infarction as well as acute ischemic changes with more pronounced ST segment elevation anteriorly and depression inferiorly than was present on tracings taken since admission.

ion. Cardiac blood pool scintigraphy may also differentiate between these two conditions. Insertion of a bolus of technetium labelled serum albumin into the antecubital vein or preferably into the pulmonary artery through a flow directed balloon catheter produces a dynamic nuclear angiogram. In the presence of a VSD the tracer appears in the right ventricle and pulmonary artery almost immediately after it appears in the left ventricle. If the physical findings are suggestive of cardiac tamponade, a flow directed balloon catheter may confirm its presence, but if the suspicion of ventricular free wall rupture is high, only cardiac catheterization with demonstration of leakage of dye on the ventriculogram can confirm and localize the tear.

The reported incidence of ventricular aneurysm following a myocardial infarction varies from 3.5% to 35% due to differences in diagnostic criteria. When defined as a protrusion of a localized portion of the external aspect of the left ventricle beyond the remainder of the cardiac surface with simultaneous protrusion of the cavity, the incidence is much closer to the lower figure. Aneurysm formation may occur acutely within the first week of a myocardial infarction or not until several months or years following infarction. Aneurysms most frequently occur in the anterior surface of the left ventricle following transmural anterior myocardial infarctions. Inadequate bed rest following infarction has been suggested to contribute to the development of ventricular aneurysms, but this has not been confirmed. Increasing congestive heart failure, serious arrhythmias, and recurrent embolic phenomenon are symptoms that should raise the possibility of aneurysm formation. Palpation may reveal an abnormal precordial pulsation. Chest radiographs may have abnormal contour of the left cardiac border including a localized bulge.[13] The electrocardiogram often reveals persistent ST segment elevation. Two dimensional echocardiography is a useful non-invasive technique for detecting aneurysms.

Pericarditis is a not infrequent cause of precordial or shoulder pain within the first week follow

new murmurs were audible no abnormal precordial pulsations were described and there was no re elevation of the CK He had two more episodes of chest pain not associated with electrocardiographic changes or CK elevation but with persistent pulmonary congestion He had no further chest pain after initiation of nitroglycerin ointment therapy but died suddenly 21 days after admission The absence of any murmurs or precordial thrill makes papillary muscle dysfunction or rupture and ventricular septal rupture unlikely causes of the cardiac decompensation Rupture of the ventricular free wall is equally unlikely for signs of cardiac tamponade should be present in a patient surviving for several days The persistent ST segment elevation suggests the presence of diffuse hypokinesis or an aneurysm A study of the natural history of ST segment elevation following acute myocardial infarction found that ST segment elevation persisting more than 2 weeks after myocardial infarction did not resolve over a 6 month follow up[11] It was associated with clinically more severe myocardial infarctions and left ventricular asynergy Other than ST segment elevation there were no other signs suggestive of pericarditis

This patient s clinical course is best explained by extension of his myocardial infarction As noted previously further myocardial necrosis has been noted in more than 50% of acute transmural myocardial infarctions at an average of 5 8 days after admission[1] After occlusion of a coronary artery the myocardial infarction in the distribution of the occluded vessel is not complete rather there is a zone of reversibly ischemic myocardium that is at risk for infarction[1] During the episodes of chest pain our patient was probably extending his infarct to include these areas of ischemic myocardium despite the absence of a re elevation of the CK It is not clear if the nitroglycerin ointment prevented further ischemic episodes or if the infarct has been completed with no further myocardium in jeopardy The persistent pulmonary congestion after the episodes of chest pain was secondary to extension of the myocardial injury further compromising cardiac function Studies are now underway to develop effective techniques of identifying patients with large areas of ischemic myocardium at jeopardy in the setting of acute myocardial infarction Interventions designed to preserve the ischemic myocardium might then successfully alter the course of patients such as the one under discussion

Autopsy findings

The heart examined after postmortem coronary arteriography and fixation in distension[1] demonstrated severe atherosclerosis with a 90% occlusion of the proximal left anterior descending coronary artery (Fig 4) The other coronary arteries had diffuse calcified atherosclerosis but no other obstructions greater than 50% of the lumen Histologic study of the region of maximum obstruction of the left anterior descending showed organizing thrombus situated over an ulcerated atherosclerotic plaque (Fig 5)

The region of heart supplied by the left anterior descending coronary artery had a massive transmural myocardial infarct (Figs 4 and 5) The infarct involved the epicardial fat and a portion of the right ventricle It extended from the anterior papillary muscle group to the junction of mid and inferior thirds of the interventricular septum The infarcted wall was markedly thinned compared to the surviving inferior and lateral wall

Histological study of the infarct showed it to be all of one age consistent with the clinical date of infarction The margins of the infarcted tissue adjacent to the surviving vascularized zones had well established granulation tissue formation The midportion of the infarct which was well removed from a vascular supply showed little evidence of resolution of the necrotic tissue (Fig 5) A small area of mural thrombus overlay the endocardium in the middle of the infarct but the majority of the endocardium showed thickening by connective tissue proliferation consistent with the infarct s age[1]

The lungs were congested and edematous Two small organizing infarcts with associated thromboemboli were present

Pathology discussion

DR GROVER M HUTCHINS The findings in the heart at autopsy show clearly that there had been but a single episode of myocardial necrosis The very large transmural anterior septal infarct was produced by thrombotic occlusion of the proximal left anterior descending coronary artery Usually in these cases the thrombus overlies an atherosclerotic plaque which has erosion or ulceration of its surface[19] The injured plaque surface and the plaque contents exposed to the circulating blood serve as a nidus for thrombosis Even in this patient where some time has elapsed since the acute event and organization and recanalization of the thrombus has occurred it is possible to

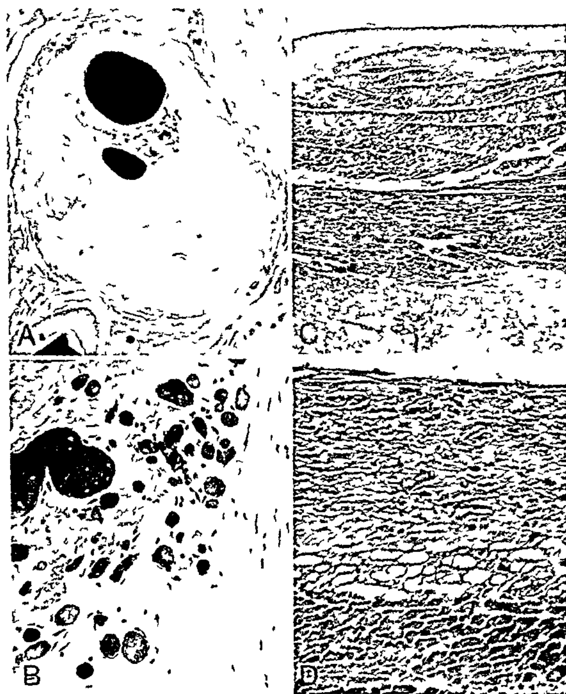


Fig 5 A through D *A* Transverse section of the left anterior descending coronary artery at the level of the arrow in Fig 4 A There are multiple channels of recanalization filled with black injection mass in the organizing thrombus (Hematoxylin and eosin original magnification ×30) *B* Channel of recanalization organizing thrombus and fibrous remnants of ruptured atherosclerotic plaque from the section shown in *A* (Hematoxylin and eosin original magnification ×300) *C* Transverse section of the anteroseptal transmural myocardial infarct from near its midportion The thinning of the wall is not explainable by reparative processes which are poorly developed in the infarct (Hematoxylin and eosin original magnification ×?0) *D* The endocardium shows marked thickening by mesenchymal cells and connective tissues in the area of the infarct The surviving subendocardial muscle is markedly vacuolated The infarcted muscle cells are eosinophilic and anucleate (Hematoxylin and eosin original magnification ×300)

new murmurs were audible no abnormal precordial pulsations were described and there was no re elevation of the CK He had two more episodes of chest pain not associated with electrocardiographic changes or CK elevation but with persistent pulmonary congestion He had no further chest pain after initiation of nitroglycerin ointment therapy but died suddenly 21 days after admission The absence of any murmurs or precordial thrill makes papillary muscle dysfunction or rupture and ventricular septal rupture unlikely causes of the cardiac decompensation Rupture of the ventricular free wall is equally unlikely for signs of cardiac tamponade should be present in a patient surviving for several days The persistent ST segment elevation suggests the presence of diffuse hypokinesis or an aneurysm A study of the natural history of ST segment elevation following acute myocardial infarction found that ST segment elevation persisting more than 2 weeks after myocardial infarction did not resolve over a 6-month follow up [11] It was associated with clinically more severe myocardial infarctions and left ventricular asynergy Other than ST segment elevation there were no other signs suggestive of pericarditis

This patient s clinical course is best explained by extension of his myocardial infarction As noted previously further myocardial necrosis has been noted in more than 50% of acute transmural myocardial infarctions at an average of 5 8 days after admission After occlusion of a coronary artery the myocardial infarction in the distribution of the occluded vessel is not complete rather there is a zone of reversibly ischemic myocardium that is at risk for infarction During the episodes of chest pain our patient was probably extending his infarct to include these areas of ischemic myocardium despite the absence of a re elevation of the CK It is not clear if the nitroglycerin ointment prevented further ischemic episodes or if the infarct has been completed with no further myocardium in jeopardy The persistent pulmonary congestion after the episodes of chest pain was secondary to extension of the myocardial injury further compromising cardiac function Studies are now underway to develop effective techniques of identifying patients with large areas of ischemic myocardium at jeopardy in the setting of acute myocardial infarction Interventions designed to preserve the ischemic myocardium might then successfully alter the course of patients such as the one under discussion

Autopsy findings

The heart examined after postmortem coronary arteriography and fixation in distension,[ ] demonstrated severe atherosclerosis with a 90% occlusion of the proximal left anterior descending coronary artery (Fig 4) The other coronary arteries had diffuse calcified atherosclerosis but no other obstructions greater than 50% of the lumen Histologic study of the region of maximum obstruction of the left anterior descending showed organizing thrombus situated over an ulcerated atherosclerotic plaque (Fig 5)

The region of heart supplied by the left anterior descending coronary artery had a massive transmural myocardial infarct (Figs 4 and 5) The infarct involved the epicardial fat and a portion of the right ventricle It extended from the anterior papillary muscle group to the junction of mid and inferior thirds of the interventricular septum The infarcted wall was markedly thinned compared to the surviving inferior and lateral wall

Histological study of the infarct showed it to be all of one age consistent with the clinical date of infarction The margins of the infarcted tissue adjacent to the surviving vascularized zones had well established granulation tissue formation The midportion of the infarct which was well removed from a vascular supply showed little evidence of resolution of the necrotic tissue (Fig 5) A small area of mural thrombus overlay the endocardium in the middle of the infarct but the majority of the endocardium showed thickening by connective tissue proliferation consistent with the infarct s age [ ]

The lungs were congested and edematous Two small organizing infarcts with associated thromboemboli were present

Pathology discussion

DR GROVER M HUTCHINS *The findings in the heart at autopsy show clearly that there had been but a single episode of myocardial necrosis The very large transmural anterior septal infarct was produced by thrombotic occlusion of the proximal left anterior descending coronary artery Usually in these cases the thrombus overlies an atherosclerotic plaque which has erosion or ulceration of its surface [15] The injured plaque surface and the plaque contents exposed to the circulating blood serve as a nidus for thrombosis Even in this patient where some time has elapsed since the acute event and organization and recanalization of the thrombus has occurred it is possible to*

recognize fibrous remnants of the atheroma in the organizing thrombus

The worsening of the patient s symptoms six days after the onset of the infarct is best explained by an expansion of the original lesion The topography of the heart as shown in Fig 1 is consistent with this interpretation The infarcted zone is markedly thinned compared to the adjacent surviving muscle thinned to a much greater degree than can be accounted for simply by the removal of necrotic muscle Also the relative positions of the anterior papillary muscle has been shifted to a more lateral position These two morphologic changes thinning of the infarct and altered topographic relationships can be accounted for by an expansion of the infarct

It is probable that the expansion occurs by an intramural tearing of the necrotic myocardium Ruptures of the ventricular wall septum or papillary muscle tend to occur at 4 to 6 days post infarction The sudden clinical worsening observed in this patient 6 days post infarction would correlate well with infarct expansion Extension of the infarct that is additional new myocardial necrosis was not observed

That the left ventricle develops worsened cardiac dysfunction as a result of infarct expansion even though no additional muscle has undergone necrosis may be secondary to the topographic changes The surviving inferior and lateral myocardium suffers a loss of curvature as a result of the expansion of the anterior septal region Effective ventricular function is dependent on an adequate thickness of myocardium arranged with appropriate curvature to translate wall tension into intracavitary pressure Infarct expansion tends to flatten parts of the functioning myocardium rendering them less able to generate pressure

Infarct expansion is of common occurrence in patients with large transmural infarcts ' In some instances the hypotension which accompanies the acute ventricular dilatation may lead to focal necroses on the margin of the infarct in the distribution of the obstructed artery These secondary lesions probably account for the serum enzyme elevations observed in some patients with this second event The electrocardiographic changes occurring at that time' may reflect simply an expanded area of infarct being presented to the precordial leads The evolution of infarct expansion originally observed in the hearts of patients studied at autopsy has now been confirmed by serial two dimensional echocardiographic studies A higher mortality rate was observed in those patients in whom there was a greater expansion of the infarct

Summary

This 57 year old man suffered a large transmural anteroseptal myocardial infarct After an initial stable period of several days he developed episodes of chest pain hypotension and congestive failure The left sided congestive failure persisted until death Study of the heart at autopsy showed that the worsened clinical state could be explained by expansion of the area of infarcted myocardium Infarct expansion may be regarded as a subtle form of myocardial rupture Intramural tearing of necrotic muscle may occur abruptly or insidiously and may lead to worsened cardiac function and symptoms and signs suggestive of new infarction The phenomenon of expansion should be distinguished from extension defined as additional myocardial necrosis since it may have important long term effects on the heart s topography and function

REFERENCES

1 Reid P R Taylor D R Kelly D T Weisfeldt M K, Humphries J O Ross R S and Pitt B Myocardial infarct exten ion detected by precordial ST-segment mapping N Engl J Med 290 123 1974
2 Wei J Ventricular septal defect complicating myocardial infarction Johns Hopkins Med J 141 95 1977
3 Hutchins G M Rupture of the interventricular septum complicating myocardial infarction Pathological analysis of 10 patients with clinically diagnosed perforations AM HEART J 97 165 1979
4 Vlodaver Z and Edwards J E Rupture of ventricular septum or papillary mu cle complicating myocardial infarction Circulation 55 815 19 7
5 Griffith G C Hegde B and Oblath R W Factors in myocardial rupture An analysis of two hundred and four cases at Los Angeles County Hospital between 1924 and 1959 Am J Cardiol 8 792 1961
6 Lewis A J Burchell, H W and Titus, J L Clinical and pathologic features of postinfarction cardiac rupture Am J Cardiol 23 43 1969
7 London R E and London S B Rupture of the heart A critical analy is of 47 consecutive autopsy cases Circulation 31 202, 1965
8 Van Tassel R A and Edward J E Rupture of heart complicating myocardial infarction Analysis of 40 cases including nine examples of left ventricular false aneurysm Chest 61 104 1972
9 Wei J Y Hutchins G M and Bulkley B H Papillary muscle rupture in fatal acute myocardial infarction A potentially treatable form of cardiogenic shock Ann Intern Med 90 149 1979
10 Dubnow M H, Burchell H B and Titus, J L Postinfarction ventricular aneurysm A clinicomorphologic and electrocardiographic study of 80 cases AM HEART J 70 753 196
11 Applebaum E and Nicolson G H B Occlusive

established working standards for vectorcardiography in 1975[5] but no real unanimity exists even now as to the best electrode *system*

To cardiologists not *primarily interested* in vectorcardiography these disagreements *on lead* systems have probably acted as a *deterrent to* clinical interest For that reason, this *review will* bypass completely a discussion *of the relative* merits of various lead systems—allowing *the read*er interested in that aspect to pursue *the appro*priate references on his own

A vectorcardiographic loop is *produced by* the simultaneous recording and combination *of* any two of the three leads (X plus Z X plus Y Y plus Z) These voltages are plotted from a central point usually on an oscilloscopic screen but in the case of the *direct writing* vectorcardiograph a moving arm *writes the loop* on an immobile piece of graph paper

Since most *electrocardiographic* information is found in the X (*left right*) *and* Z (posterior anterior) directions *it is not* surprising that the X Z combination (horizontal *transverse* or XZ plane) has the greatest *diagnostic power* The X Y combination is designated *as the frontal* plane, and the Y Z combination is designated as the *sagittal plane* which may be viewed from either the *right or left*

Since these loops *are a* plot of voltage against voltage elapsed *time must* be indicated by interruption of the *otherwise* continuous recording at predetermined intervals *such as* 1 2 2.5 5 or 10 msec each The *tracing is* interrupted in such a way that each *segment of the* loop has a distinct leading or trailing *edge*, *whose blunt* or pointed end indicates the directional *movement of the* loop as a whole

If the XYZ *leads* are recorded on magnetic tape the loops *may be generated* later from any set of simultaneous *complexes* and this taped information may *then be* subjected also to signal averaging noise *reduction* and computer analysis storage and retrieval

In its simplest form *vectorcardiography* has many disadvantages The *superimposition of* P QRS and T loops causes serious difficulty in evaluating *and timing* initial and terminal QRS forces However *the use of* gating circuits now available in the *current* commercially available units permits selective recording of isolated P QRS or T loop Thus the overlap problem has been largely eliminated

The *high gains* used in vectorcardiography readily introduce artifacts and 60 Hz interference especially in the Y axis These problems can be generally overcome by meticulous care of electrodes and cable tips proper skin preparation and careful grounding of the patient and the vectorcardiographic equipment

Location of the vectorcardiographic department far away from high voltage electrical equipment such as x ray machines and a comfortable bed for the patient (to decrease muscle movement) are also desirable Despite these precautions however occasional patients cannot be *recorded* without confusing interference

Bedside vectorcardiography is eminently possible and is performed in many institutions However it is even more often beset with technical problems as bedridden patients may be attached to other electrical equipment which causes interference and such patients are frequently uncooperative In addition vectorcardiographic equipment readily breaks down especially when moved about excessively Probably for these reasons vectorcardiographic study of acute ECG problems (such as acute myocardial infarction) are relatively few Nevertheless VCG s have even been recorded during exercise[4 6 7 8]

Vectorcardiograms are commonly recorded at very high amplification (5 cm to 40 cm per millivolt) The very high amplifications are used for study of P and T loops To the extent that the diagnostic power of vectorcardiography depend on this high amplification which facilitates precise time and voltage measurements equivalent results are entirely possible using standard leads with similar amplification

The development of the corrected lead systems has encouraged quantitative analysis of the XYZ leads and of the vectorcardiographic loops. These measurements may be made manually or by computer but the unique diagnostic power of the VCG lies in the directional and rotary characteristics of loops the so called phase relationships which result from the combination of voltages from the three lead axes

This review will be largely concerned with the qualitative description of P QRS and T loops in a variety of clinical situations rather than with the more quantitative aspects except for some simple quantitative criteria and measurements which can be derived manually As Witham has stated the analysis of a VCG by an experienced

undamentals of clinical cardiology

linical vectorcardiography in adults Part 1

win Hoffman M D
u Hyde Park and Far Rockauav N Y

he classic 12 lead electrocardiogram (ECG) emains the standard display method for surface ardiac electrical activity Another display the ectorcardiogram (VCG) despite an extensive terature developed over almost 30 years and the eady commercial availability of vectorcardio raphic equipment is employed in relatively few nstitutions Even when available it is usually mployed in only a small minority of cardiac atients

This review is directed to the cardiologist whose raining and interests may not have included ectorcardiography but who may now seek an utline of current knowledge literature and pplications of this technic

The author plans to keep constantly in mind he message implied in the paper by Eliot and ssociates entitled Loops for the Lost An Intro luctory Lesson for Vector Electrocardiographic Enjoyment (If not Proficiency and Accuracy)

Several excellent sources on vectorcardiogra hy are available in standard textbook form rogrammed or atlas formats and also in review rticles and audio cassettes The texts by Chou nd co workers and by Cooksey and colleagues nclude sections devoted entirely to pediatric spects emphasizing congenital heart disease Published symposia include sections on surface napping and computer analysis This review owever will be devoted to the current status of linical vectorcardiography in adult patients

The most simplistic approach to the VCG ssumes that all cardiac electrical activity (P QRS ST and T) originates from a single point (E) located in the anatomic center of the chest and conducted homogeneously to the surface In that situation an anatomically oriented electrode system would yield reliable X (left positive right negative) Y (foot positive head negative) and Z (posterior positive anterior negative) leads which would necessarily display all the data recordable by any surface electrode system

Unfortunately for vectorcardiographers the heart does not behave like a simple dipole gener ator immersed in a sphere filled with saline Accordingly a variety of lead systems have been described which either ignore or correct the inhomogeneities and compartmentalizations of the human heart

The corrected systems prescribe the location of seven or more electrodes modify the voltages obtained by means of resistances and then com bine the modified voltages in order to produce appropriate X Y and Z axis potentials The correction results in a three lead (XYZ) ECG which those surface voltages would represent in a 150 pound male subject with an idealized torso

Thus errors in correction are inherently present in large or small persons or in those with thoracic deformities and probably also in those with cardiac enlargement The basic assumptions also break down when the conductivity of the thoracic contents is greatly altered from the normal as in the case of emphysema

The Frank seven electrode lead system is almost universally used presently in the United States but serious workers have championed other systems have compared systems to one another and have even compared day to day variations and the effects of electrode placement in various interspaces and in various body posi tions and phases of respiration [3 5 3] A special committee of the American Heart Association

F om the D p rtm nt of Card ol gy Lo g I l nd J w h Hill ide Medi al Ce te N w Hyd Park N Y d th Department of C rdi l gy S uth Shore Divis on St J hn Ep scop l Hospital Fa Rockaw y N Y

Rec i ed f r publ c t on M h 14 1979

Repri t req ests Irwin Hoffm M D Lo g I l d C d scul r Gro p P C 123 G o e A e Ced hurst N Y 11516

established working standards for vectorcardiography in 1975 [5] but no real unanimity exists even now as to the best electrode system

To cardiologists not primarily interested in vectorcardiography these disagreements on lead systems have probably acted as a deterrent to clinical interest For that reason this review will bypass completely a discussion of the relative merits of various lead systems—allowing the reader interested in that aspect to pursue the appropriate references on his own

A vectorcardiographic loop is produced by the simultaneous recording and combination of any two of the three leads (X plus Z X plus Y Y plus Z) These voltages are plotted from a central point usually on an oscilloscopic screen but in the case of the direct writing vectorcardiograph a moving arm writes the loop on an immobile piece of graph paper

Since most electrocardiographic information is found in the X (left right) and Z (posterior anterior) directions it is not surprising that the X Z combination (horizontal transverse or XZ plane) has the greatest diagnostic power The X Y combination is designated as the frontal plane and the Y Z combination is designated as the sagittal plane which may be viewed from either the right or left

Since these loops are a plot of voltage against voltage elapsed time must be indicated by interruption of the otherwise continuous recording at predetermined intervals such as 1 2 2 5 5 or 10 msec each The tracing is interrupted in such a way that each segment of the loop has a distinct leading or trailing edge whose blunt or pointed end indicates the directional movement of the loop as a whole

If the XYZ leads are recorded on magnetic tape the loops may be generated later from any set of simultaneous complexes and this taped information may then be subjected also to signal averaging noise reduction and computer analysis storage and retrieval

In its simplest form vectorcardiography has many disadvantages The superimposition of P QRS and T loops causes serious difficulty in evaluating and timing initial and terminal QRS forces However the use of gating circuits now available in the current commercially available units permits selective recording of isolated P QRS or T loops Thus the overlap problem has been largely eliminated

The high gains used in vectorcardiography readily introduce artifacts and 60 Hz interference especially in the Y axis These problems can be generally overcome by meticulous care of electrodes and cable tips proper skin preparation and careful grounding of the patient and the vectorcardiographic equipment

Location of the vectorcardiographic department far away from high voltage electrical equipment such as x ray machines and a comfortable bed for the patient (to decrease muscle movement) are also desirable Despite these precautions however occasional patients cannot be recorded without confusing interference

Bedside vectorcardiography is eminently possible and is performed in many institutions However it is even more often beset with technical problems as bedridden patients may be attached to other electrical equipment which causes interference and such patients are frequently uncooperative In addition vectorcardiographic equipment readily breaks down especially when moved about excessively Probably for these reasons vectorcardiographic study of acute ECG problems (such as acute myocardial infarction) are relatively few Nevertheless VCGs have even been recorded during exercise [63,6,9]

Vectorcardiograms are commonly recorded at very high amplification (5 cm to 40 cm per millivolt) The very high amplifications are used for study of P and T loops To the extent that the diagnostic power of vectorcardiography depends on this high amplification which facilitates precise time and voltage measurements equivalent results are entirely possible using standard leads with similar amplification

The development of the corrected lead systems has encouraged quantitative analysis of the XYZ leads and of the vectorcardiographic loops These measurements may be made manually or by computer but the unique diagnostic power of the VCG lies in the directional and rotary characteristics of loops the so called phase relationships which result from the combination of voltages from the three lead axes

This review will be largely concerned with the qualitative description of P QRS and T loops in a variety of clinical situations rather than with the more quantitative aspects except for some simple quantitative criteria and measurements which can be derived manually As Witham[1] has stated the analysis of a VCG by an experienced

observer requires only a few minutes and one or two simple measurements.

The normal QRS loop (references 2 to 40)

Vectorcardiographic notation can sometimes be confusing and many different kinds of terminology are used by different workers to describe the same thing. The simplest descriptive terms are *direction* and *rotation*.

Since the horizontal or transverse loop is derived from a combination of the X (left right) and Z (posterior anterior) axes, those four directions plus the designations *clockwise* or *counterclockwise* are really sufficient for almost all descriptive purposes.

Thus it may be simply stated that in the normal horizontal plane QRS loop the earliest forces are generally right and anterior followed by counterclockwise movement left and anterior which usually is completed by 30 to 35 msec.

Then the loop proceeds left and posterior where the maximum vectors are located and still with counterclockwise rotation. The loop finally returns to the E point after terminal rightward forces are commonly inscribed posteriorly. The time dashes are frequently close together indicating slight conduction delay for the first 20 msec and the last 30 msec of the QRS loops. The duration of the loops in the normal usually does not exceed 100 msec. However with tape recording techniques and high amplification occasional normal values up to 120 msec have been observed.[4]

The maximum voltage in the horizontal plane rarely exceeds 2.0 millivolts in the normal. Standardization is usually inscribed as a 1 or 0.5 millivolt equivalent adjacent to each loop submitted for interpretation.

Inspection of a few normal vectorcardiograms in any of the general references will permit even a novice to familiarize himself quickly with normal loops. In the frontal (X Y) reference plane the directions are of course left right and inferior superior and the rotations are again clockwise or counterclockwise. In this plane however the normal rotation varies according to the direction of the major QRS vector. If the QRS loop lies along the X axis or close to it ("horizontal" position) the loop will normally exhibit counterclockwise rotation. On the other hand if the major QRS vector lies more or less along the Y axis ("vertical") position the normal loop will exhibit clockwise rotation. In the intermediate position roughly at +45 degrees in the frontal plane the loops are commonly rather narrow and may exhibit figure of eight shapes or may display clockwise or counterclockwise movement. An important variant of normal is frequently seen in the frontal plane especially in young women of slender body build. The major QRS vector may be directed along or even to the right of the Y axis producing a "vertical" position. The initial forces are commonly leftward rather than to the right and the entire loop is inscribed clockwise. The initial leftward forces are above the X axis so that Q waves are inscribed in scalar Lead Y and also in Leads 3 and F of the conventional electrocardiogram. This loop is similar in some respects to loops seen in inferior divisional block and in right ventricular hypertrophy. It may also be confused on occasion with the frontal loop of inferior myocardial infarction.

When the vectorcardiographer has described the horizontal and frontal loops he has utilized information from all three (X Y and Z) axes and theoretically no additional information can be derived from the last combination (Y Z)—the sagittal reference plane.

It naturally follows from the above considerations that when the sagittal reference plane is viewed from the right the initial forces will be anterior the major forces posterior and the rotation will be clockwise.

The value of recording loops in all three projections lies in the possibility that initial or terminal forces may be perpendicular to one of the reference planes and therefore not be recorded well if at all in that particular plane.

The vast majority of vectorcardiographic interpretations however can be made from inspection and measurement of the horizontal and frontal loops only—the sagittal reference plane being used for confirmatory purposes.

Although variations in QRS loop magnitudes have been described related to sex race and body build these variations are rather small. However in an occasional case it is important to realize that voltages tend to be smaller in women and larger in males especially blacks. Greater voltage variations are encountered in the vectorcardiograms of infants children and adolescents.[37, 3] Here the relative thinness of the chest wall plays an important role. The normal voltages for the various reference planes at different ages have

tal plane and generally exhibits counterclockwise rotation.[1] These T loop abnormalities as well as other varieties of repolarization disorders will be discussed in a separate section devoted to T loops.

Right ventricular hypertrophy (references 2 to 16, 56 to 74)

As has been discussed above, the normal QRS loop represents a "levo" vectorcardiogram owing to the normal domination of QRS activity by the left ventricle. It is not surprising, therefore, that in only very advanced right ventricular hypertrophy will the resulting QRS loop be oriented completely anterior and rightward—the electrical *position of* the right ventricle. In lesser degrees of right ventricular hypertrophy, a shift of the QRS either anteriorly or to the right occurs, but usually with preservation of some leftward QRS forces and with preservation of the counterclockwise rotation in the horizontal plane, which is characteristic of the normal left ventricular QRS loop.

These several features have become the basis of Chou and associates' classification of right ventricular hypertrophy. The classic or severe type, in which the loop is oriented both to the right and anterior in the horizontal plane and with reversal of rotation from counterclockwise to clockwise, has been designated as Type A. This variety is seen commonly in congenital heart disease in children, especially with pressure overloads as in pulmonic valve stenosis. When seen in an adult, *for example*, with cor pulmonale or mitral stenosis, one may be sure that the pulmonary artery pressure is extremely high. Type B right ventricular hypertrophy is characterized by an anterior addition of QRS forces, usually in the first half of the loop and with little or no addition of rightward forces. This results in an anterior counterclockwise QRS loop in the horizontal plane which is oriented to the left and anterior of the E point. In general, Type B RVH loops are encountered with milder degrees of right ventricular hypertrophy than Type A. In the Type C variety, anterior forces are minimal and the major alteration from normal is the addition of rightward forces, usually in the middle and terminal portions of the QRS. The normal counterclockwise rotation is preserved, and of course the addition of rightward forces decreases the maximum leftward voltage while the maximum rightward voltage increases, especially terminally.

This variety of QRS loop is frequently seen in acquired right ventricular hypertrophy in adults, especially in cor pulmonale and in mitral stenosis.

Although many published quantitative criteria are available for the identification of right ventricular hypertrophy, the following have proven to be of the greatest value in the author's experience:

1. Maximum rightward voltage of 1.0 millivolts or greater.
2. The left/right millivolt ratio less than 1.0.
3. The percentage of loop area in the right posterior quadrant of the transverse plane exceeds 20% of the total QRS loop area.
4. The anterior and rightward QRS loop area in the transverse plane exceeds 70% of the total area.
5. The QRS loop area in the right inferior quadrant of the frontal plane exceeds 20% of the total area.

As in the case of left ventricular overloads, attempts have been made to identify diastolic or systolic overloads on the basis of various VCG patterns. Two decades of experience have convinced most workers that such separations are simply not possible. In the case of pure pressure overload on the right side, there is little doubt that the rightward voltages bear a close relationship to the right ventricular systolic pressure and may be predictive of pulmonic valve gradient in cases of pulmonic valvular stenosis. However, in the frequent combinations of right ventricular obstruction with other lesions such as shunts, attempts at pressure estimation are often misleading.

The greatest difficulties in the vectorcardiographic diagnosis of right ventricular hypertrophy lie in two special circumstances:

1. The counterclockwise anterior horizontal loop which may resemble the loop of dorsal myocardial infarction or a very similar loop seen commonly in persons without heart disease of any kind. This problem will be discussed in a subsequent section as "anterior conduction delay."
2. The problem of loops which have some characteristics of right ventricular conduction delay (terminal slowing oriented to the right, either anterior or posterior) but with significant anterior or rightward orientation of major QRS vectors. Here the separation between a pure conduction delay and conduction delay asso-

angle the distal half of the QRS loop may exceed in area the proximal half and the time at which maximum QRS forces are achieved may be delayed [1]

These vectorcardiographic features are particularly valuable when voltage criteria for left ventricular hypertrophy are not satisfied Although values of 2 0 millivolts or greater in the horizontal plane are strongly suggestive in adults of left ventricular hypertrophy such voltages are commonly not achieved even when the scalar 12 lead ECG satisfies standard voltage criteria This discrepancy probably results in the Frank system from the attenuation of uncorrected torso voltages by the resistances employed especially at the apical or V_4 position which frequently is the site of the greatest voltage found on the torso Attenuation may also result when the cube or tetrahedral lead systems are used owing to the remoteness of the electrodes from the precordium

Despite the lack of sensitivity to decreased voltage the other QRS loop characteristics of LVH described above are frequently valuable guides to diagnosis However it must be admitted that as far as voltage criteria are concerned the scalar 12 lead ECG is a more sensitive detector of left ventricular hypertrophy than is the vectorcardiogram

Caution must be used in interpreting high voltage QRS loops in children or adolescents The thin chest wall and relatively large heart frequently result in high QRS voltages in the absence of anatomic abnormality The over all QRS duration in left ventricular hypertrophy may frequently reach 120 msec but the rotational characteristics do not resemble left bundle branch block and the time dashes are evenly spaced quite dissimilar from the clustering effect seen in bundle branch disturbances

Several studies have correlated hemodynamics and left ventricular mass with vectorcardiographic measurements [5]

Ishizawa and associates correlated the vectorcardiogram with left ventricular mass determined angiographically while Bennett and Evans made similar correlations with echocardiographic measurements

In both studies maximum vectorcardiographic voltages especially in the horizontal plane correlated *extremely* well with left ventricular mass determined as mentioned above Ellison and Restieaux have reviewed the correlations between right or left ventricular hemodynamic load and the vectorcardiogram while Yankopoulous and associates[3] made similar studies in 257 patients with clinical aortic valvular disease

Again although many vectorcardiographic measurements were used the most effective were horizontal plane or spatial voltages and the R wave peak time in lead X

However Yankopoulous and colleagues confirmed the difficulty of finding criteria which would separate systolic overload left ventricular hypertrophy (aortic stenosis) from volume overload left ventricular hypertrophy (aortic regurgitation)

No reliable criteria enabling separation were found and it seems reasonable at this stage of knowledge to be satisfied with the diagnosis of an abnormal QRS loop indicative of left ventricular hypertrophy or left ventricular overload without specifying whether the ventricle has been subjected to increased volume or pressure work An additional qualitative characteric of left ventricular hypertrophy loops is the tendency for the normal initial anterior rightward forces (found in approximately 85% of normals) to be replaced by initial anterior leftward forces This characteristic is present in approximately 60% of patients with hypertension or aortic valvular disease No completely satisfactory explanation for this initial shift has been established although several have been proposed In the author s view simple early leftward posterior addition would naturally reduce or even eliminate the normal right anterior or initial forces and could account for the observed changes without invoking anatomical shifts of the interventricular septum or septal fibrosis or infarction

The frontal QRS loop in left ventricular hypertrophy is most commonly located inferior to the X axis and to the left of the E point Thus an abnormal superior axis is not a feature of left ventricular hypertrophy However the loops commonly lie close to the X axis and in this position as in normal loops occupying similar positions the rotation is counterclockwise The voltage criteria for hypertrophy in the frontal reference plane is also approximately 2 millivolts especially if the patient is over 40 years of age In younger patients a value of 2 4 millivolts should be exceeded in order that left ventricular hypertrophy be diagnosed

The T loop in left ventricular hypertrophy is oriented to the right and anterior in the horizon

rior forces will include associated right ventricular hypertrophy associated dorsal infarction or associated anterior conduction delay [9,10] and this will be discussed in a subsequent section devoted to prominent anterior forces

When the horizontal QRS loop suggests right ventricular hypertrophy because of prominent anterior forces (Type B) or because of anterior and clockwise rotation (Type A) [78] and the frontal loop does not exhibit the expected clockwise rotation but is instead inscribed counterclockwise associated left ventricular hypertrophy should be considered [9,8] In these instances if the counterclockwise rotation in the frontal plane is associated with an abnormal superior axis right ventricular hypertrophy with associated superior divisional block or its equivalent would be the preferred diagnosis

Ventricular septal defect in infancy is an interesting model of biventricular hypertrophy with varying degrees of right ventricular enlargement depending upon the restrictive characteristics of the septal defect In a non restrictive defect the right ventricle operates against systemic pressure and the most severe type of right ventricular hypertrophy results All gradations of relative right and left ventricular hypertrophy are thus possible in this entity Riggs and associates [4] have described vectorcardiographic patterns in the horizontal plane which suggest the presence of non restrictive defects As one might expect these are the patterns of more severe right ventricular hypertrophy In one such pattern the horizontal loop is completely anterior rightward and entirely clockwise while in the second pattern suggesting a non restrictive defect only the mid portion of the QRS loop exhibits counterclockwise rotation with the entire loop anterior to the E point the significant terminal rightward forces and a terminal appendage are inscribed clockwise

The scalar electrocardiographic equivalent of the Katz Wachtel phenomenon is found in the vectorcardiographic loop in the horizontal plane characteristic of left ventricular hypertrophy but with prominent anterior forces exceeding 0 6 millivolts The scalar precordial leads in such instances would display very large biphasic complexes and are thus suggestive of biventricular hypertrophy

Gamboa and [illegible] have compared the vectorcardiogr[illegible] orthogonal electrocardiograms of 87 patients [illegible] necropsy evidence of biventricular hypertrophy to both normals and to patients with left ventricular hypertrophy or right ventricular hypertrophy They have published useful scalar criteria for separating th BVH cases from normal and for separating BV cases respectively from LVH or from RVH

Prominent anterior QRS forces (references 85 to 101)

So far in this review changes in voltage ar axis shift have been described as resulting onl from hypertrophy of the right or left ventricle However as mentioned earlier in the discussio entirely similar axis shifts may occur as a result subtraction (as infarction) or from conducti delay—in which the QRS axis shifts in the dire tion of the impaired conduction One of the ear promises of vectorcardiography was the appare ability to recognize true posterior or dorsa infarction [85,87] In such cases the subtraction posteriorly directed QRS forces would result in anterior shift of QRS loops Although the prec dial scalar leads in such cases would continue show R waves as they do normally the change precordial leads might be limited to a broadeni of the R waves in Leads V_1 V and V contrast the vectorcardiographic loop wo show a major shift in direction anterior and the left of the F point

As vectorcardiography developed and beca more quantitative with the introduction of c rected lead systems actual quantitative crite were proposed for the recognition of true posterior infarction [87] when prominent anterior loops were encountered and were unaccompanied by evidence for inferior or lateral infarction—in which cases of course the diagnosis of adjacent dorsal infarction was relatively easy

These concepts were proven incorrect with the advent of coronary arteriography and by contrast ventriculography With these techniques it became apparent that many patients presenting with prominent anterior QRS loops had either perfectly normal coronary arteries or inappropriately placed coronary disease—most frequently in the left anterior descending artery Clearly some other explanation was needed

These difficulties were recognized by several authors notably by Kennedy and associates and by Ha and colleagues who pointed out that the prominent anterior horizontal QRS loops of patients with proven dorsal infarction were in

ciated with right ventricular hypertrophy may be difficult indeed The classic problem is presented by patients suspected of atrial septal defect and who present with scalar ECG s manifesting RSR complexes in Lead V and a picture of incomplete right bundle branch block In such cases a clear separation even by vectorcardiogram between RVH and pure right ventricular conduction delay may be difficult In the absence of terminal conduction slowing and with loops oriented largely anterior to the E point a diagnosis of moderate RVH as seen in atrial septal defect is warranted However when only terminal conduction delay is present so that pure right ventricular conduction defect must be diagnosed atrial septal defect is by no means ruled out

The problems attending the diagnosis of right ventricular hypertrophy in the presence of right bundle branch block will be dealt with in the section on right bundle branch block

The frontal QRS loop in right ventricular hypertrophy of either Types A or C is oriented inferior to the E point with clockwise rotation and prominent terminal forces to the right The Type B frontal loop lacking late prominent rightward forces may be entirely normal

Certain vectorcardiographic changes may occur in emphysema even in the absence of significant right ventricular hypertrophy These changes result from the over inflation of the lungs and the more vertical position of the heart resulting from descent of the diaphragms

The electrical QRS forces tend to become oriented along the Y axis and a prominently inferior or superior axis may be observed In addition the interposition of overexpanded lung tissue between the heart and the chest electrodes may result in a marked attenuation of the anterior QRS forces producing a picture reminiscent of anterior infarction and sometimes making that diagnosis difficult to exclude Thus in a vectorcardiogram presenting with decreased amplitude and duration of anterior forces coupled with an abnormally superior or inferior frontal axis a diagnosis of emphysema could logically be supported in the presence of appropriate clinical information while in the absence of such data an incorrect diagnosis of anterior infarction could easily be made The reader is reminded of the basic assumptions of vectorcardiography referred to in the introduction In emphysema and in chest deformities such as kyphoscoliosis these basic assumptions—only approximations at best—break down and a qualitative descriptive approach to the QRS loops may be preferable to more quantitative analysis

The T loop in right ventricular hypertrophy is most commonly oriented to the left and usually exhibits clockwise rotation In the Type A loops the T loop is usually posterior and sometimes markedly so In the Type C loop the T loop orientation may be somewhat more leftward but the clockwise rotation is usually maintained Unfortunately for differential diagnosis by vectorcardiogram the T loops in right bundle branch block are identical to those of right ventricular hypertrophy This problem will be discussed in the section on T loops

The atrial vectorcardiogram is often of value when the QRS loops suggest right ventricular hypertrophy A P loop characteristic of left atrial overload in the presence of right ventricular enlargement by VCG always suggests mitral valve disease In contrast right atrial overload in the presence of right ventricular hypertrophy calls attention to a purely right sided problem P loops will be discussed in a separate section of this review

Biventricular hypertrophy (references 2 to 16 75 to 84)

Inasmuch as left ventricular hypertrophy adds left or posterior forces or both while right ventricular hypertrophy adds anterior or rightward forces or both it follows that in some instances such additions may be mutually cancellable and the resulting QRS loop may be entirely normal In most instances however vectorcardiographic clues may suggest the presence of biventricular hypertrophy although no really firm diagnostic criteria have been established which have stood the test of time

When the vectorcardiogram is characteristic of left ventricular hypertrophy because of high leftward voltage the presence of prominent large right posterior forces exceeding 20% of the total horizontal loop area should raise the question of the presence of right ventricular hypertrophy as well[7]

In a horizontal loop quite characteristic of left ventricular hypertrophy very large anterior forces exceeding 0 6 millivolts should call for additional explanation As usual with such loops the differential diagnosis for the prominent ante

Many perplexing problems in vectocardiography such as right bundle branch block with very prominent anterior forces or superior divisional block with prominent anterior forces are much better approached if the possibility of anterior conduction delay is kept in mind This will often allow the vectorcardiographer to avoid the pitfalls of mistaken diagnoses of associated dorsal infarction or right ventricular hypertrophy especially when the clinical picture indicates that neither diagnosis is likely

In the following sections on conduction disorders and on myocardial infarction frequent reference will be made to the problem of prominent anterior QRS forces and the content of the present section will be assumed as standard information

Myocardial infarction and pseudo infarction (references 2 to 16 102 to 160)

An extensive literature on the QRS loop abnormalities resulting from myocardial infarction is available in the textbooks atlases and symposia listed as general references in the first section of this review

Useful tabulations of quantitative criteria as well as excellent diagrams of the QRS loop abnormalities in infarctions of various location may be found in the texts by Chou and associates by Cooksey and colleagues and by Witham as well as in papers by Gunnar and co workers[10] by Van Herpen and associates[19] and by Eddleman and Pipberger[1] The classic findings in infarctions of significant size are easy to recognize and little dispute exists about diagnostic criteria The fundamental effect of an infarction is the subtraction of QRS potentials from the infarcted area resulting in a QRS shift in a direction away from the area of QRS potential loss

This subtraction effect which is maximal in the first half of the QRS loop but may spare the initial 01 or 02 sec segment in some cases results in an unexpected bowing or convexity of the loop away from the infarcted zone

For example in inferior myocardial infarction the first half of the QRS loop is characteristically displaced superiorly and to the left with an upward convexity away from the diaphragmatic location of the infarction This results in a clockwise rotation of a rather transversely placed frontal loop—a marked contrast to the usual counterclockwise rotation in that electrical position[1] If the initial 01 or 02 sec of the QRS loop are spared by the infarction and remain directed inferiorly the upward bowing effect between 20 and 40 or 50 msec is still quite evident and the diagnosis is apparent in the VCG

Thus the diagnosis of inferior infarction from the frontal plane vectorcardiogram can be easily established, even in the presence of R waves in Leads 3 and aV_F of the conventional scalar electrocardiogram[110, 111] The most useful quantitative criteria are a superior position of the 30 msec vector and an X intercept of the QRS loop located 0 3 millivolts or greater from the E point[11]

Very similar considerations govern the genesis of the abnormal horizontal loops in anterior myocardial infarction

Here as a result of anterior necrosis with a corresponding subtraction effect on the QRS loop the initial forces are directed posteriorly in marked contrast to the normal right and anterior position

In anteroseptal infarctions the 01 and 02 sec vectors are posterior while in more strictly anterior infarction the 01 or 02 sec vectors may remain anterior and right with subsequent posterior shift after 02 sec Some early clockwise rotation is common These loops which exhibit deformity after completion of the initial forces, thus are similar qualitatively to the inferior infarction loops in which the deformity develops after 02 sec[13]

In many anterior infarctions the normal counterclockwise rotation of the bulk of the horizontal loop is preserved However in more extensive infarctions and especially in those with a lateral component the rotation of the loop changes to clockwise[138, 13]

With lateral wall infarction the major change occurs in the loops which include the X axis (horizontal and frontal) The initial forces are abnormally rightwards exceeding the normal 022 sec duration for rightward forces

In the case of the frontal plane these exaggerated rightward forces commonly exhibit counterclockwise rotation (whereas in the normal such vertical forces usually rotate clockwise)

In the horizontal plane the abnormal rightward forces may be directed anteriorly if the lateral infarction is associated with dorsal involvement or posteriorly if the association is with anterior infarction In all of these instances the changes in direction and rotation of the loops

tinguishable from very similar loops found in patients proven by invasive techniques to be free of coronary disease or right ventricular hypertrophy

Some authors devoted themselves to establishing criteria which would distinguish between right ventricular hypertrophy and pure posterior infarction but did not attempt to separate these pathological conditions from the normal variant which was frequently encountered and which produced an identical QRS abnormality[90]

Until the mid 1970s the anatomical and functional divisions of the left bundle branch were generally considered as hemi divisions with the left bundle presumably dividing into a superior anterior branch and an inferior posterior branch Rosenbaum and colleagues[4] introduced and popularized the concept of electrocardiographic hemiblock as well as the concept that the entire intraventricular conducting system formed a *trifascicular* system when the right bundle branch was included along with the two subdivisions of the left bundle branch

The term hemiblock unfortunately implies that no room is left for other divisions or fascicles However the anatomic work of Demoulin and Kulbertus[5] and others has established that the anatomic *structure of the left bundle branch* instead of two equal divisions is extremely variable and most often includes a third anterior or septal fascicle Although great variation was encountered in the anatomic dissections of left bundle branch systems performed by Demoulen and Kulbertus[9] it was apparent that this anterior fascicle was sometimes a direct extension of the left main bundle sometimes a branch of the superior fascicle and sometimes a branch of the inferior fascicle

Thus an anatomic basis was laid for the concept that *anterior conduction delay might be the cause for some of the puzzling instances of* prominent anterior QRS loops in the demonstrated absence of right ventricular hypertrophy or of coronary disease with true posterior infarction [90]

Convincing evidence that this is indeed the case has come from two directions The first has been the production of prominent anterior QRS forces with atrial stimulation with the aberration disappearing at slower heart rates In these experiments which have been reported by three separate groups of investigators (Kulbertus and associates Cohen and colleagues[95] and Reiffel and Bigger[k]) other types of abberration such as right bundle branch block superior divisional block etc were also produced at different coupling intervals Although Reiffel and Bigger entitled their paper Pure anterior conduction delay A variant fascicular defect they do not attribute the delay to a disorder of conduction in any specific new fascicular subdivision but Kulbertus and colleagues believe that impaired conduction in the septal fascicle is indeed the cause for the observed abberration and anterior shift of the QRS

Hoffman and co workers[101] have described prominent anterior QRS loops in patients whose only coronary pathology was in the anterior descending artery In two such cases following unsuccessful coronary artery bypass surgery anterior myocardial infarction developed with a complete loss of the pre existing prominent anterior forces In the cases reported no coronary disease of vessels supplying the posterior wall or ventricular contraction defect of the posterior wall was observed[1]

It thus seems more than reasonable that at least in some cases prominent anterior forces may result from a conduction disorder probably *in the anterior or septal fascicle of the left bundle* branch as well as from right ventricular hypertrophy or from true dorsal myocardial infarction This concept is important because prominent anterior forces may be encountered combined with bundle branch block fascicular block myocardial infarction or ventricular hypertrophy It becomes necessary therefore to consider anterior conduction delay as the possible mechanism for prominent anterior forces whenever it is encountered—not only when it occurs in the pure form which originally led to the overdiagnosis of true posterior myocardial infarction *The concept of anterior conduction delay is supported by additional* logical force Since it is well known and accepted that conduction delay may shift the QRS to the right (right bundle branch block) to the left and posterior (left bundle branch block) superiorly (superior divisional block) or inferiorly (inferior divisional block) it would seem unreasonable that shift in an anterior direction could not occur just as easily especially as strong anatomic evidence for anterior fascicles has been presented

cardiomyopathies pulmonary emphysema and both left and right ventricular hypertrophies These causes of pseudo infarction in the vector cardiogram will be discussed separately

REFERENCES

1 Eliot R S Everhart F J and Sterns L P Loops for the lost An introductory lesson for vector-electrocardiographic enjoyment (if not proficiency and accuracy) Arch. Intern Med 120 293 1967
2 Cooksey J D., Dunn M., and Massie E Clinical Vectorcardiography and Electrocardiography Second Edition Chicago Ill 1977 Yearbook Medical Publishers Inc
3 Chou T C Helm R A and Kaplan S Clinical Vectorcardiography Second Edition New York, 1974 Grune & Stratton Inc
4 Witham A C A System of Vectorcardiographic Interpretation Chicago Ill 1975 Yearbook Medical Publishers Inc
5 Kennedy R J., Varriale P and Alfenito J C Textbook of Vectorcardiography New York 19 0 Harper & Row
6 Benchimol A. Vectorcardiography Baltimore 1973 The Williams & Wilkins Company
7 Lemberg L. and Castellanos A Jr Vectorcardiography Second Edition A Programmed Introduction New York, 1975 Appleton Century Crofts Inc
8 Reddy C V R and Gould L A Correlative Atlas of Vectorcardiograms and Electrocardiograms Mount Kisco New York 1977 Futura Publishing Co
9 Chung E K Vectorcardiography Self Assessment Hagerstown Md 1974 Harper & Row
10 Benchimol A and Desser K B Advances in clinical vectorcardiography Am J Cardiol 36 76 19 5
11 Chou T C Value and limitations of vectorcardiography in cardiac diagnosis Cardiovasc Clin 6 163 1975
12 Constant J Learning Electrocardiography Chapter in Vector Loops and the Vectorcardiogram Boston 19 3 Little Brown & Company
13 Benchimol A Vectorcardiography Supplement Tape Number One Accel Series American College of Cardiology Bethesda Md
14 Hoffman I and Taymor R C Eds Vectorcardiography 1965 Amsterdam 1966 North Holland Publishing Company
15 Hoffman I Hamby R I and Glassman E Eds Vectorcardiography 2 Amsterdam 1971 North Holland Publishing Company
16 Hoffman I and Hamby R I Eds Vectorcardiography 3 Amsterdam 19 6 Elsevier North Holland Publishing Company
17 Burch G E DePasquale N P and Cronvich J A A standard reference [illegible] for [illegible] vectorcardiography Comparison [illegible] the [illegible] hedron and the Frank systems Am Heart J [illegible]
18 Witham A C The [illegible] recorded with sponge electrodes Am Heart J 7 [illegible]
19 McFee R and Parung [illegible] A [illegible] orthogonal lead system for clinical electrocardiography Am Heart J 62 93 1961
20 Grishman A and Scherlis L Spatial Vectorcardiography Philadelphia 1952 W B Saunders Company
21 Frank E An accurate clinically practical system for spatial vectorcardiography Circulation 12 3 1956
22 Langner P H Jr Okada R H Moore S R and Fies H L Comparison of four orthogonal systems of vectorcardiography Circulation 17 46 1958
23 Brody D A and Arzbaecher R C A comparative analysis of several corrected vectorcardiographic leads Circulation 19 533 1964
24 Pipberger H V McCaughan D Littman D Pipberger H A Cornfield J Dunn R A Batchlor C D and Berson A S Clinical Application of a Second Generation Electrocardiographic computer program Am J Cardiol 35 597 19 5
25 Report of Committee on Electrocardiography American Heart Associations Recommendations for Standardization of Leads and of Specifications for Instruments in Electrocardiography and Vectorcardiography Circulation 52 11 1975
26 Draper H W Peffer G J Stallman F W Littman D and Pipberger H V The corrected orthogonal electrocardiogram and vectorcardiogram in 510 normal men (Frank lead system) Circulation 30 853 1964
27 Bristow J D A study of the normal Frank vectorcardiogram Am Heart J 61 242 1961
28 Beswick F W, Jordan R C and Kilpatrick G S Normal orthogonal vectorcardiographic data Am J Cardiol. 16 321 1965
29 Forkner C E Hugenholtz P G and Levine H D The vectorcardiogram in normal young adults Frank lead system Am Heart J 48 36 1954
30 Lyon A F and Belletti D A The Frank vectorcardiogram in normal men Br Heart J 30 1 3 1968
31 McCall B W Wallace A G and Estes E H Jr Characteristics of the normal vectorcardiogram recorded with the Frank lead system Am J Cardiol 10 514 1962
32 Pipberger H V Goldman M J Littman D Murphy G P Cosma J and Snyder J R Correlations of the orthogonal electrocardiogram and vectorcardiogram with constitutional variables in 518 normal men, Circulation 35 536 1967
33 Sotobata I Richman H and Simonson E Sex differences in the vectorcardiogram Circulation 37 438 1968
34 Witham A C and Lahman J E Vectorcardiogram past forty Am Heart J 79 149 1970
35 Willems J L Poblete P F and Pipberger H V Day to day variation of the normal orthogonal electrocardiogram and vectorcardiogram Circulation 45 10 1972
36 Copeland G D McEachran A B Smith H W and Brody D A The McFee Parungao (axial) vectorcardiogram in normal subjects Am Heart J 85 4 1973
37 Liebman J Lee M H Rao P S and Mackay W Quantitation of the normal Frank and McFee Parungao orthogonal electrocardiogram in the adolescent Circulation 48 735 1973
38 Ruekkinen H, and Rautaharju P Body position electrode level and respiration effects on the Frank lead electrocardiogram Circulation 53 40 19 6
39 Borun E R Sapin S O and Goldberg S J Scalar amplitude measurements of data recorded with cube

is dramatic and obvious and with a little practice, expertise can be achieved by any cardiologist familiar with standard electrocardiographic diagnosis and with the normal appearance of QRS loops as described previously.

These rather standard vectorcardiographic abnormalities have been correlated with clinical diagnoses of myocardial infarction (based on ECG criteria and enzymatic measurements) with coronary arteriography and ultimately with contrast ventriculography as well.[1, 10, 113, 179] In general rather good correlations have been observed between the classic loop abnormalities described above and with appropriately located coronary artery obstructions and areas of ventricular asynergy and akinesia.[133, 134, 13] In a study of 102 consecutive patients whose right anterior oblique left ventriculograms showed severe asynergy in the anterior and apical segments, 84 presented with horizontal QRS loops characteristic of anterior infarction but with clockwise rotation in the horizontal plane.[1] In another study patients with inferior myocardial infarction presenting with unexpectedly low ejection fractions were found by vectorcardiography to present additional evidence for anterior infarction not apparent in the standard 12 lead scalar ECG.

Thus it seems possible that some correlation of the vectorcardiogram with infarct size and with residual myocardial function can be made although it appears likely that such correlation will be crude at best. In experimental infarction with serial vectorcardiograms available direct approximations of infarct weight have been possible although this is seldom a situation which pertains clinically.

Much more difficulty is present in the analysis of the distal half of QRS loops especially the importance of small distortions called bites. Normally the QRS loops are inscribed smoothly and without sudden changes in rotation. The earliest workers in vectorcardiography correlated distal bites with autopsy evidence of myocardial scarring[1] and a theoretical basis for the phenomenon was developed by Selvester and colleagues[1] who constructed a computer model for the normal vectorcardiogram and were able to show that subtraction of small segments (as little as one % of the total) would result in bites similar to those observed clinically. Distal abnormalities have been correlated with infarctions in the diaphragmatic surface.

The clinical vectorcardiographer fortunately will usually encounter such bites when the proximal portion of the QRS loops exhibits classic deformities characteristic of infarction as described above. The real difficulty lies when such bites are detected in the absence of more proximal abnormalities. Witham has suggested that before significance is attached to such deviations they be identified in at least two planes, have a minimum duration of six msec and a minimal deviation of 0.1 millivolts.

Such bites are almost never found in normal young subjects but in contrast are fairly common in patients with angina, hyperlipidemia, diabetes and hypertension. Witham's text includes a valuable tabulation of distal QRS loop abnormalities resulting from infarctions in all areas.

Although the available literature indicates rather good correlations between the vectorcardiogram and clinical autopsy, arteriographic and ventriculographic evidence of myocardial infarction many difficulties nevertheless remain. The problem of large anterior loops which may result from true posterior infarction has already been discussed. However it should be pointed out that the diagnosis of true isolated posterior infarction is really quite unusual. Generally posterior infarction is associated with inferior or lateral infarction and the combination is easy to recognize.[1] The vectorcardiographer should be wary when the *only* abnormality found is an anterior QRS loop as the patient may be entirely free of coronary disease, his QRS loop representing anterior conduction delay as previously discussed.

Horizontal QRS loops with prominent anterior forces are easily recognized as they are displaced into the left anterior quadrant of the horizontal reference plane. Certain quantitative descriptors may be used to identify these loops. The anterior voltage measured on the Z axis reaches 0.5 millivolts or greater. The half area vector is ten degrees or more anterior to the X axis and maximum anterior forces are achieved at 30 msec or later. In addition the total duration of anterior QRS forces exceeds 42 msec. Unfortunately identical quantitative characteristics are found in patients with anterior conduction delay and dorsal infarction so that the differential diagnosis cannot be made on the basis of the vectorcardiographic characteristics.

Myocardial infarction may be mimicked by a variety of cardiac disorders, the most common are

ventricular systolic pressure in pulmonary stenosis from combined vectorcardiographic data Am HEART J 86 318 1973
73 Walston A Harley A and Pipberger H V Computer analysis of the orthogonal electrocardiogram and vectorcardiogram in mitral stenosis Circulation 50 472 1974
74 Toyama J Okada A Nagata Y Okajima M and Yamada K Electrocardiographic change in pulmonary emphysema Effects of experimentally induced over inflation of the lungs on QRS complexes Am HEART J 87 606 1974
75 Pagnoni A and Goodwin J F The cardiographic diagnosis of combined ventricular hypertrophy Br Heart J 14 451 1952
76 Rosenman R H Krause S Hwany W and Katz L N Electrocardiographic diagnosis of combined left and right ventricular strain Am HEART J 40 453 19 0
77 Varriale P Kennedy J W and Alfenito J C Vectorcardiogram of combined ventricular hypertrophy Posterior counterclockwise loop (Frank system) Br Heart J 31 457 1969
78 Papadopoulos C Lee Y C and Scherlis L Isolated ventricular septal defect Electrocardiographic vector cardiographic and catheterization data Am J Cardiol 16 359 1965
79 Wolff R Morse R L and Mazzoleni A Combined ventricular hypertrophy in Vectorcardiography 1965 Hoffman I and Taymor R C, eds Amsterdam 1966 North Holland Publishing Co
80 Kovatas Hopff L and Wyss O A M Vectorcardiographic signs of biventricular hypertrophy Cardiologia (Basel) 48 269 1966
81 Toscano Barbosa E and DuShane J W Ventricular septal defect Correlation of electrocardiographic and hemodynamic findings in 60 proved cases Am J Cardiol 3 721 1959
82 Muster A J Kardatzke J L and Paul M H Vectorcardiographic patterns of combined ventricular hypertrophy in infancy and children in Vectorcardiography 1965 Hoffman I and Taymor R C eds Amsterdam 1966 North Holland Publishing Co p 279
83 Gamboa R Klingeman J D and Pipberger H V Computer diagnosis of biventricular hypertrophy from the orthogonal electrocardiogram Circulation 39 72 1969
84 Riggs T Mehta S Hirschfeld S Borkat G and Liebman J Ventricular septal defect in infancy A combined vectorcardiographic and echocardiographic study Circulation 59 385 19 9
85 Rothfeld E I Berstein A Wachtel F W and Karlen W S The vectorcardiogram in direct posterior wall myocardial infarction Am J Cardiol 7 496 1961
86 Gray J Corbin M King J and Dunn M Diagnostic value of vectorcardiogram in ... the posterior infarction Am HEART J 34 ... 197?
87 Hoffman I Taymor R C Morris M H and Kittell I Quantitative criteria for the diagnosis of dorsal infarction using the Frank vectorcardiogram Am HEART J 70 ...
88 Ha D, Kraft D I and Stein P D The anteriorly oriented horizontal vector loop The problem of distinction between direct posterior myocardial infarction and normal variation Am HEART J 88 408 1974
89 Kennedy R J Alfenito J C and Schwartz M S Direct posterior myocardial infarction in Vectorcardiography 3 Hoffman I and Hamby R I ed Amsterdam 1976 Elsevier North Holland Publishing Co p 29
90 Kini P M and Pipberger H V Criteria for electrocardiographic differentiation of right ventricular hypertrophy from pure posterior myocardial infarction Am J Cardiol 33 608 1974
91 Mathur V S and Levine H D Vectorcardiographic differentiation between right ventricular hypertrophy and posterobasal myocardial infarction Circulation 42 883
92 Kramer N E Chawla K K Patel R Khan M Mayer I and Towne W D Differentiation of posterior myocardial infarction from right ventricular hypertrophy and normal anterior loop by echocardiography Circulation 58 1057 1978
93 Hilsenrath J Hamby R I and Hoffman I Pitfalls in the prediction of coronary artery disease from the electrocardiogram or vectorcardiogram J Electrocardiol 6 291 1973
94 Rosenbaum M B Elizari M V and Lazzari J O The Hemiblocks New Concepts of Intraventricular Conduction Based on Human Anatomical Physiological and Clinical Studies Oldsmar Fla 19 0 Tampa Tracings
95 Demoulin J C and Kulbertus H E Histopathological examination of concept of left hemiblock Br Heart J 34 807 1972
96 Cohen S I Lau S H Stein E Young M W and Damato A N Variations of aberrant ventricular conduction in man Evidence of isolated and combined block within the specialized conduction system An electrocardiographic and vectorcardiographic study Circulation 38 899 1968
97 Kulbertus H E de Leval Rutten F and Casters P Vectorcardiographic study of aberrant conduction Anterior displacement of QRS Another form of intraventricular block Br Heart J 38 549 1976
98 Nakaya Y Hiasa Y Murayama Y Ueda S Nagao T Niki T Mori H and Takashima Y Prominent anterior QRS force as a manifestation of left septal fascicular block J Electrocardiol 11 39 1978
99 Reiffel J A, and Bigger J T Pure anterior conduction delay A variant fascicular defect J Electrocardiol 11 315 19 8
100 Hoffman I Mehta, J Hilsenrath J and Hamby R I Anterior conduction delay A possible cause for prominent anterior QRS forces J Electrocardiol 9 15 1976
101 Suzuki K and Toyama S Vectorcardiographic criteria of high posterior infarction Differentiation from normal subject right ventricular hypertrophy and primary myocardial disease J Electrocardiol 11 159 1978
102 Hugenholtz P G Forkner C E Jr and Levine H D A clinical appraisal of the vectorcardiogram in myocardial infarction II The Frank system Circulation 24 825 1961

and Frank leads from normal children Circulation 39 859 1969

40 Rautaharju P M Punsar S Blackburn H Warren J and Menotti A Waveform patterns in Frank lead rest and exercise electrocardiograms of healthy elderly men Circulation 48 541 19 3

41 Abbott Smith C W and Chou T C Vectorcardiographic criteria for the diagnosis of left ventricular hypertrophy AM HEART J 79 361 19 0

42 Romhilt D W Greenfield J C Jr and Estes E H Jr Vectorcardiographic diagnosis of left ventricular hypertrophy Circulation 37 15 1969

43 Varriale P Alfenito J C and Kennedy R J The vectorcardiogram of left ventricular hypertrophy Analysis and criteria (Frank lead system) Circulation 33 569 1966

44 Brackbill T A and Shah P M Vectorcardiographic comparison of left ventricular hypertrophy in idiopathic hypertrophic subaortic stenosis aortic stenosis and aortic regurgitation AM HEART J 88 269 1974

45 McCaughan D Littman D and Pipberger H V Computer analysis of the orthogonal electrocardiogram and vectorcardiogram in 939 cases with hypertensive cardiovascular disease AM HEART J 85 4?7 19 3

46 Cabrera E and Gaxiola A Diagnostic contribution of the vectorcardiogram in hemodynamic overloading of the heart AM HEART J 60 ?96 1960

47 Hugenholtz P G and Gamboa R Effect of chronically increased ventricular pressure on electrical forces of the heart A correlation between hemodynamic and vectorcardiographic data (Frank system) in 90 patients with aortic or pulmonic stenosis Circulation 30 511 1964

48 Wallace A G McCall B W and Estes E H Jr The Vectorcardiogram in left ventricular hypertrophy A study using the Frank lead system AM HEART J 63 466 196?

49 Sobrino J A Mate I Codina J Rico J and Sobrino N Vectorcardiograms in severe aortic insufficiency Clockwise rotation Dis Chest 67 568 1975

50 Ishizawa K Ishizawa K Motomura M Konishi T and Wakabayashi A High reliability rates of spatial pattern analysis by vectorcardiogram in assessing the severity of eccentric left ventricular hypertrophy AM HEART J 91 50 1976

51 Bennett D H and Evans D W Correlation of left ventricular mass determined by echocardiography with vectorcardiographic and electrocardiographic voltage measurements Br Heart J 36 981 1974

52 Ellison R C and Restieaux N J Quantitation of ventricular hypertrophy and hemodynamic load with vectorcardiogram Progr Cardiovasc Dis 14 559 1972

53 Yankopoulous N A Haisty W K and Pipberger H V Computer analysis of the orthogonal electrocardiogram and vectorcardiogram in 257 patients with aortic valve disease AM J Cardiol 40 707 1977

54 Postell W N Rainey F L Witham A C and Edmonds J H Jr Vectorcardiographic and electrocardiographic manifestations of increasing left ventricular pressure overload AM HEART J 77 33 1969

55 Browne P J Sridhar S Desser K B Benchimol A and Sheasby C Hypertrophy or dilatation? A vectorial analysis of echocardiographically determined left ventricular enlargement J Electrocardiol 11 117 1978

56 Chou T Masangkay M P Young R Conway G F and Helm R A Simple quantitative vectorcardiographic criteria for the diagnosis of right ventricular hypertrophy Circulation 48 126? 1973

57 Rasmussen K and Sarland S J Prediction of right ventricular systolic pressure in pulmonary stenosis from combined vectorcardiographic data AM HEART J 86 318 1973

58 McCaughan D Koroxenides G T Kopff L G and Williams C New vectorcardiographic criteria for the diagnosis of acquired right ventricular hypertrophy Comparison with standard electrocardiographic criteria Circulation 28 766 1963

59 Hugenholtz P G and Gamboa R Effect of chronically increased ventricular pressure on the electrical forces of the heart Correlation between hemodynamic and vectorcardiographic data (Frank lead system) in 90 patients with aortic pulmonic stenosis Circulation 30 511 1964

60 Lee Y C and Scherlis L Some problems in the vectorcardiographic diagnosis of right ventricular hypertrophy *in* Hoffman I ed Vectorcardiography 1965 Amsterdam 1966 North Holland Publishing Co., p 142

61 Gamboa, R Hugenholtz P G and Nada A Corrected (Frank) uncorrected (cube) and forces in right ventricular hypertension Br Heart J 28 62 1966

62 Lasser R P Borun E R and Grishman A Spatial vectorcardiographic differentiation between right ventricular hypertrophy as seen in congenital heart disease AM HEART J 42 370 1951

63 Taymor R C Hoffman I and Henry E The Frank vectorcardiogram in mitral stenosis A study of 29 cases Circulation 30 865 1964

64 Walsh T J Roman G T Jr., and Massie E The vectorcardiographic QRSsE loop findings in chronic cor pulmonale AM HEART J 60 59? 1960

65 Walston A Harley A and Pipberger H V Computer analysis of the orthogonal electrocardiogram and vectorcardiogram in mitral stenosis Circulation 50 472 1974

66 Graf W S Gunther L and Allenstein B QRS pattern in mitral stenosis Am J Cardiol 14 266 1964

67 Watanabe Y Nishijima K Richman H and Simonson E Vectorcardiographic and electrocardiographic differentiation between cor pulmonale and anterior wall myocardial infarction AM HEART J 84 20? 1972

68 Selvester R H and Rubin H B New criteria for the electrocardiographic diagnosis of emphysema and cor pulmonale AM HEART J 69 437 1965

69 Toyama S Comparative study of the vectorcardiogram in pulmonary emphysema and mitral stenosis, Ann Rep Center Adult Dis Osaka 1 48 1961

70 Walsh T J The vectorcardiogram in cor pulmonale Progr Cardiovasc Dis. 9 363 1967

71 Kerr A Adicoff A Klingman J D and Pipberger H V Computer analysis of the orthogonal electrocardiogram in pulmonary emphysema Am J Cardiol 25 34 1970

72 Rasmussen K and Sorland S J Prediction of right

vectorcardiogram in patients with segmental areas of akinesia or dyskinesia on left ventricular angiogram Adv Cardiol 16 246 1976

134 Young E Cohn P F Gorlin R Levine H D and Herman M V Vectorcardiographic diagnosis and electrocardiographic correlation in left ventricular asnergy due to coronary artery disease I Severe asynergy of the anterior and apical segments Circulation 51 467 1975

135 Hilsenrath J Tabrah F Hamby R I and Hoffman I Relation of left ventricular contractile patterns in coronary artery disease to the electrocardiogram and vectorcardiogram J Electrocardiol 8 335 1975

136 Starr J W Wagner G S, Draffin R M Reed J B Walston A II and Behar V S Vectorcardiographic criteria for the diagnosis of anterior myocardial infarction Circulation 53 229 1975

137 Mehta J Hoffman I Smedresman P Hilsenrath J and Hamby R I Vectorcardiographic electrocardiographic and angiographic correlations in apparently isolated inferior wall myocardial infarction AM HEART J 91 699 1976

138 Howard P F Behchmol A Desser K B Reich F D and Graves C Correlation of electrocardiogram and vectorcardiogram with coronary occlusion and myocardial contraction abnormality Am J Cardiol 38 582 1976

139 Zoneraich O and Zoneraich S A vectorcardiographic study of spatial P QRS and T loops in diabetic patients without clinically apparent heart disease J Electrocardiol 10 207 1977

140 Estes E H Jr Whalen R E Stewart S R Jr and McIntosh H D The electrocardiographic and vectorcardiographic findings in idiopathic hypertrophic subaortic stenosis AM HEART J 65 155 1963

141 Flowers N and Horan L Electrocardiographic and vectorcardiographic features of myocardial disease *in* Fowler N I ed Myocardial Diseases New York 1973 Grune & Stratton Inc pp 181 212

142 McCaughan D and William C The Frank electrocardiogram and vectorcardiogram in idiopathic hypertrophic subaortic stenosis *in* Wenger R ed Actuelle Probleme der Vectorkardiographie Stuttgart 1968 George Thieme Verlag p 240

143 Stein P D Solis R M Brooks, H L Matson J L and Hyland J W Vectorcardiogram simulating myocardial infarction in idiopathic hypertrophic subaortic stenosis Dis Chest 54 489 1968

144 Hamby R I and Raia F Vectorcardiographic aspects of primary myocardial disease in 50 patients AM HEART J 76 304 1968

145 Phillips H R Starr J W Behar V S Walton A Greenfield J C Jr and W[illegible] Evaluation of vectorcardiographic criteria [illegible] the diagnosis of myocardial infarction in the presence [illegible] ventricular hypertrophy Circulation 53 [illegible]

146 Nelson [illegible] Hodkin B [illegible] R A and Angelakos E T The difference vector Assessment [illegible] effects of changes or interventions AM HEART J 95 290 1978

147 Flowers N and Horan L Electrocardiographic and vectorcardiographic features of myocardial diseases, in Fowler N L ed Myocardial Diseases, New York 1973 Grune & Stratton Inc

148 Chen C H and Kawai C Anterior QRS loop in hypertrophic cardiomyopathy J Electrocardiol 11 129 1978

149 Tavel M E and Fisch C Abnormal Q waves simulating myocardial infarction in diffuse myocardial disease AM HEART J 68 534 1964

150 Ronana, J A Jr Perloff J D Bowen P J and Mann O The vectorcardiogram in Duchenne's progressive muscular dystrophy AM HEART J 84 5?? 1972

151 Klein M D Mathur V., Levine H D and Gorlin R. Electromechanical correlations in hypertrophic subaortic stenosis Circulation 38 635 1968

152 Rosenthal A Restieaux N J and Feig S A. Influence of acute variations in hematocrit on the QR[S] complex of the Frank electrocardiogram Circulation 44 456 1971

153 Anderson W T Brundage B H and Cheitlin M D Vectorcardiographic changes following coronary artery bypass surgery AM HEART J 87 491 1974

154 Aintablian A Hamby R I Hoffman I Weiss D Voleti C and Wisoff B G Significance of new Q waves after bypass grafting Correlations between graft patency ventriculogram and surgical venting technique AM HEART J 94 479 1978

155 McNeill G P Poirier N Morin J and Klassen G A. Myocardial infarction after aortocoronary saphenous vein bypass Vectorcardiographic study Br Heart J 39 903 1977

156 Howard P F Benchimol A Desser K B Reich F D and Graves C Correlation of electrocardiogram and vectorcardiogram with coronary occlusion and myocardial contraction abnormality Am J Cardiol 38 582 1976

157 Arnsdorf M F Electrocardiogram in hyperkalemia Electrocardiographic pattern of anteroseptal myocardial infarction mimicked by hyperkalemia induced disturbance of impulse conduction Arch Intern Med 136 1161 1976

158 Kini P M Eddleman E E Jr and Pipberger H V Electrocardiographic differentiation between left ventricular hypertrophy and anterior myocardial infarction Circulation 42 875 1970

159 Cha S D., Gooch A S Yang S S and Goldberg H The vectorcardiogram in prolapsed mitral leaflet myocardiopathy J Electrocardiol 7 37 1974

160 Wickline S A. and McNamara J J Vectorcardiographic quantification of infarct size in baboons, Circulation 47 910 1977

103 Gunnar R M Moran J F Sinno M Z and Shah D Vectorcardiographic diagnosis of myocardial infarction and left ventricular hypertrophy in Vectorcardiography 3 Hoffman I and Hamby R I ed Amsterdam 1976 North Holland Publishing Co p 7 20
104 Pipberger H V Computer diagnosis of the electrocardiogram and vectorcardiogram in Vectorcardiography 3 Hoffman I and Hamby R H eds Amsterdam 1976 North Holland Publishing Co p 161 169
105 Gunnar R M Pietras R J Blackaller J Dadmun S E, Szanto P B and Tobin J R Jr Correlation of vectorcardiographic criteria for myocardial infarction with autopsy findings, Circulation 35 158 1967
106 Hoffman I Taymor R C Morris M H and Kittell I T loop rotation in ischemic heart disease in Hoffman I ed Vectorcardiography 1965 Amsterdam 1966 North Holland Publishing Co p 181
107 Burch G E Horan L G, Ziskind J and Cronvich J A A correlative study of postmortem electrocardiographic and spatial vectorcardiographic data in myocardial infarction Circulation 18 325 1958
108 Van Herpen G Bruschke A V G and Hanssen A W The correlation between the coronary arteriogram and other diagnostic parameters, in Vectorcardiography 2, Hoffman I ed Amsterdam 1971 North Holland Publishing Co p 352
109 Walsh T J, Tiongson P M Stoddard E A and Massie E The vectorcardiographic QRSsE loop findings in inferoposterior myocardial infarction AM HEART J 63 516 1962
110 Young E and Williams C The frontal plane vectorcardiogram in old inferior myocardial infarction Criteria for diagnosis and electrocardiographic correlation Circulation 37 604 1968
111 Young E Levine H D Pantel S V Kemp H G Williams R A and Gorlin R The frontal plane vectorcardiogram in old inferior myocardial infarction II Mid to-late QRS changes Circulation 42 1143 1970
112 Hoffman I Taymor R C, and Gootnick A Vectorcardiographic residua of inferior infarction Seventy eight cases studied with the Frank system Circulation 29 56 1964
113 Maron B J Selvester R H and Ellis E J Selective cine coronary arteriography and vectorcardiographic diagnoses Correlative study of 100 patients, AM HEART J 82 63 1971
114 Selvester R H Kalaba R Collier C R Bellman R and Kagiwada H A digital computer model of the vectorcardiogram with distance and boundary effect Simulated myocardial infarction AM HEART J 74 792 1967
115 Toutouzas P Hubner P Samani G and Shillingford J Value of vectorcardiogram in diagnosis of posterior and inferior myocardial infarctions Br Heart J 31 629 1969
116 Witham A C VCG pattern of myocardial scarring in the absence of diagnostic Q waves in Schlant R C and Hurst J W eds Advances in Electrocardiography New York 1972 Grune & Stratton Inc
117 Beamer V Amidi M and Scheuer J Vectorcardiographic findings simulating myocardial infarction in aortic valve disease J Electrocardiol 3 71 1970
118 Murata K, Matsushita S Kurihara H, and Seki M Some pitfalls of vectorcardiographic diagnosis of myocardial infarction with particular respect to emphysema Circulation 35 172 1967
119 Ruskin J Whalen R E and Orgain E S Electrocardiogram and vectorcardiogram simulating myocardial infarction in patients with pectus excavatum and straight back, Am J Cardiol 21 446 1968
120 Benchimol A and Barreto E C Serial vectorcardiograms with the Frank system in patients with acute inferior wall myocardial infarction J Electrocardiol 2 159 1969
121 McCaughan D and Williams C Usefulness of vectorcardiography in the diagnosis of "atypical" myocardial infarctions I True posterior myocardial infarction Circulation 24 992 1961
122 Lee G B Wilson W J Amplatz K and Tuna N Correlation of vectorcardiogram and electrocardiogram with coronary arteriogram Circulation 38 189 1968
123 Benchimol A Maia I G and Tippit H Correlation of the Frank vectorcardiogram with selective coronary angiography in normal subjects and patients with coronary disease in Wenger R, ed Aktuelle Probleme der Vektorkardiographie Stuttgart 1968 George Thieme Verlag p 236
124 Mathur V S and Levine H D The separation of right ventricular hypertrophy from posterobasal myocardial infarction of a combined vectorcardiographic approach in Wenger R, ed, Aktuelle Probleme der Vektorkardiographie Stuttgart 1968 George Thieme Verlag p 237
125 Eddleman E E and Pipberger H V Computer analysis of the orthogonal electrocardiogram and vectorcardiogram in 1 002 patients with myocardial infarction AM HEART J 81 608 1971
126 Levine H D Young E and Williams R A Electrocardiogram and vectorcardiogram in myocardial infarction Circulation 45 457 1972
127 Stein P D and Simon A P Vectorcardiographic diagnosis of diaphragmatic myocardial infarction Am J Cardiol 38 568 1976
128 Starr J W Wagner G S, Behar V S Walston A II and Greenfield J C Jr Vectorcardiographic criteria for the diagnosis of inferior myocardial infarction Circulation 44 829 1974
129 Maron B J Selvester R H and Ellis E J Selective cine coronary arteriography and vectorcardiographic diagnoses Correlative study of one hundred patients, AM HEART J 82 163 1971
130 McConahay D R, McCallister B D Hallermann F J and Smith R E Comparative quantitative analysis of the electrocardiogram and the vectorcardiogram Circulation 42 245 1970
131 Hilsenrath J Hamby P K, Glassman E and Hoffman I Pitfalls in prediction of coronary arterial obstruction from patterns of anterior infarction on electrocardiogram and vectorcardiogram Am J Cardiol 29 164 1971
132 Lee G B Wilson W J Amplatz K, and Tuna, N Correlation of vectorcardiogram and electrocardiogram with coronary arteriogram Circulation 38 189 1968
133 McCaughan D, Turini G and Pipberger H V Computer analysis of the Frank electrocardiogram and

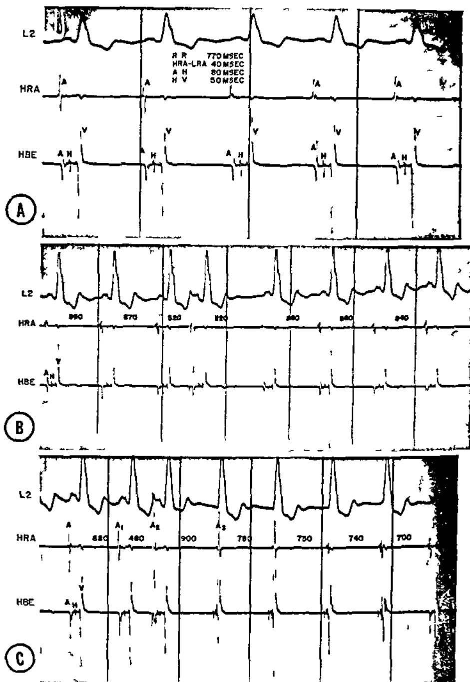


Fig 6 (Patient 5) The effect of atropine on the sinoatrial node From the top down Lead II high right atrial electrogram *(HRA)* His bundle electrogram *(HBE)* *A* the PR subintervals are normal except for an increase in the HRA LRA interval to 40 msec *B* an artificial premature beat is followed by a full compensatory pause *C* after administration of 1 0 mg of atropine the atrial premature beat is followed by a full compensatory pause which is terminated by an AV junctional rhythm at a slightly slower rate than the sinus rhythm The last beat is a fusion between the sinus and AV junctional beat

of the sinus node occurred simultaneously in this patient However it should be pointed out that there are also other explanations for the paradoxical effect of atropine on the automaticity of the sinus node as previously discussed[5]

b Atropine in the evaluation of ischemic heart disease Cokkinos and associates[42] showed that higher ventricular rates induced by atrial pacing after the administration of atropine led to an increase in ST segment depression and the incidence of angina pectoris in patients with angiographically proved CAD

The effect of atropine on cardiac arrhythmias and conduction Part 2

Paul Schweitzer MD FACC
Herbert Mark MD FACC
Bronx N Y

II Diagnostic use of atropine

a Sinus node dysfunction The nonspecific nature of the clinical symptoms caused by sinus node dysfunction and the low sensitivity of the electrophysiological findings indicate a need for additional tests to facilitate the diagnosis of sinus node dysfunction[35, 9, 81] Atropine may satisfy this need[35]

In patients with sinus bradycardia caused by sinus node dysfunction atropine in doses of 1 to 2 mg does not increase the sinus rate by more than 10 to 15 beats/minute and never over a rate of 90/minute[29, 3] *On the other hand when sinus* bradycardia is caused by extracardiac factors atropine exerts a marked positive chronotrophic effect This use of the drug in the diagnosis of sinus node dysfunction has been recently challenged by Dighton who was not able to confirm this difference in the response to atropine

Atropine produces sustained AV junctional rhythm in some patients with sinus node dysfunction Although this arrhythmia developed in a small number of patients with symptomatic sinus node dysfunction its occurrence will support the diagnosis of sinus node dysfunction Two unusual effects of atropine on sinus node recovery time may further aid in the diagnosis of this disorder Paradoxical prolongation of the sinus node recovery time[50, 51] and the replacement of sinus rhythm by AV junctional rhythm when atrial pacing is suddenly stopped also substantiate the diagnosis

The possibility of improved sinoatrial conduction and unmasking of abnormal sinus node automaticity after the administration of atropine is suggested in the following patient A 72 year old woman with a history of paroxysmal atrial fibrillation was hospitalized because of syncope The ECG showed sinus rhythm and LBBB The resting electrophysiological measurements were normal except for a high low right atrial interval which was prolonged to 40 msec (normal 25 msec) (Fig 6A) Atrial premature beats introduced before the administration of atropine did not reset the SA node regardless of the coupling interval (Fig 6B) This finding was consistent with a first degree SA block[4] Administration of atropine accelerated the heart rate from 69/minute to 88/minute During measurement of sinoatrial conduction time atrial premature beats introduced in late diastole (89% to 96% of the spontaneous sinus cycle) were followed by a full compensatory pause (Fig 6C) However the sinus node was suppressed and the return rhythm was AV junctional after atrial premature beats with a shorter coupling interval The AV junctional beats occurred following the expected full compensatory pause The mechanism underlying this effect of atropine is not clear but we believe that because atropine abolished the sinoatrial conduction disturbance the premature atrial impulses penetrated into the sinus node and suppressed it This mechanism is similar to the one which was used for the explanation of the paradoxical effect of atropine on the sinus node recovery time[50, 5] If our hypothesis is correct then an abnormal automaticity and conductivity

From the Cardiology Section Department of Medicine Bronx Veterans Administration Medical Center Mount Sinai School of Medicine New York, N Y and Jersey City Medical Center Jersey City and New Jersey Medical School Newark N J

Received for publication Feb 20 1980

Reprint requests Paul Schweitzer MD Cardiology Section Bronx VA Medical Center 130 West Kingsbridge Rd Bronx N Y 10468

0002-8703/80/080255 + 07$00 70/0 © 1980 The C V Mosby Co

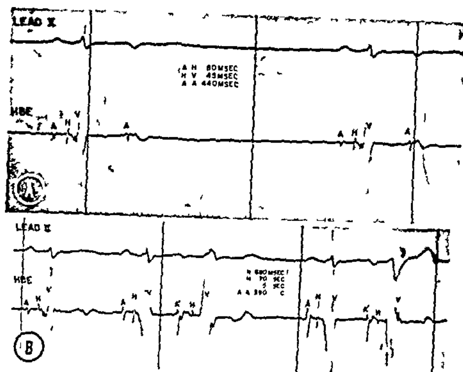


Fig 8 (Patient 7) The effect of atropine on atrial premature beats *A* Lead II and His bundle electrogram *(HBE)* show sinus beats *alternating with blocked* atrial premature beats *B* following administration of 0.5 mg of atropine the sinus rate accelerates and the conduction through the AV node improves permitting the conduction of *atrial premature beats* The *QRS* complexes of the atrial premature beats are wide because of aberrant conduction

only for patients in the coronary care unit but also *prior to* hospitalization for patients with acute myocardial *infarction* [27]

Subsequently experimental findings [7,8] and case reports [91] *challenged* the routine use of atropine in patients with acute myocardial infarction and asymptomatic bradycardia First it was shown that atropine itself *may increase* ventricular irritability [92] and that increased vagal tone is not *necessarily* harmful in experimental myocardial *infarction* [87,9] or in patients with myocardial infarction [93] At the same time Epstein and co workers pointed out that while atropine suppresses so called *benign* ventricular premature beats it is less *effective* in the therapy of malignant ventricular premature beats The effect of atropine on *hypotension* was also questioned Finally the possible *adverse effect* of increased heart rate on the *size of* myocardial infarction also came into *consideration* *In other words* uncontrolled tachycardia caused by *atropine* may increase the size of the infarct and this *led* to doubts *about the usefulness* of the drug

The possible adverse effect of atropine and the *experimental findings* noted above suggested a need for re evaluation or redefinition of the r of atropine in managing patients with acu myocardial infarction Despite a number of co trary recommendations we believe that the use atropine in acute myocardial infarction is st justified [95,96] and it remains the drug of choice patients in whom sinus node suppression is com plicated by hypotension or increased ventricul irritability The drug is not indicated however uncomplicated sinus bradycardia and shoul probably not be given without medical superv sion Because the adverse effects of atropine ar dose related [25] it is important that the dose of th drug be kept between 0 4 and 0 8 mg It has bee shown by Chadda and colleagues [26] that i patients with acute myocardial infarction dose of 0 8 mg or less are usually not associated wit increased ventricular irritability Unanswered however is the question whether patients who d not respond to lower doses of atropine should be treated by insertion of a temporary pacemaker o with increasing doses of atropine At this time we prefer to use a temporary pacemaker in these nonresponsive patients

The clinical effectiveness of atropine in

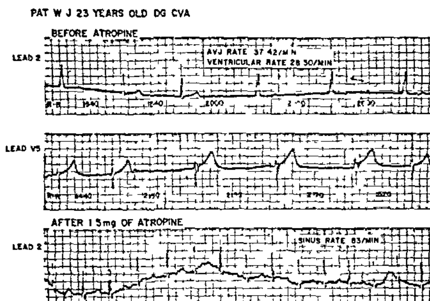


Fig 7 (Patient 6) The effect of atropine on the sinoatrial node Leads II and V recorded before the administration of atropine show a slightly irregular AV junctional rhythm with alternating idioventricular beats After the administration of atropine a sinus rhythm resumes

c Normalization of Wolff Parkinson White syndrome Since the original description of the Wolff Parkinson White (W P W) syndrome it has been known that atropine can restore a normal QRS complex in some patients with this syndrome This effect is unpredictable however[5, 8] Normalization of W P W syndrome after atropine occurs in subjects in whom the drug facilitates conduction through the AVN and decreases the ERP of the AVN Refractoriness and conduction through the AVN become shorter than through the accessory pathway and therefore activation of the ventricles occurs by way of the normal pathway This effect is of clinical significance mainly in patients with suspected myocardial infarction The ECG of W P W syndrome not only simulates myocardial infarction but also masks the presence of an acute myocardial infarction Normalization of the QRS complex therefore reveals information of diagnostic value in patients with suspected myocardial infarction and the W P W syndrome

III Therapeutic indications for atropine

a Sinus node dysfunction Administration of atropine is indicated in patients with sudden onset of sinus node suppression complicated by hypotension or increased ventricular irritability The indication for atropine is less certain in patients with chronic symptomatic sinus node dysfunction It is possible that atropine or other long acting parasympatholytic drugs may be of some benefit in patients in whom for any reason a permanent pacemaker is not implanted

The effects of atropine in a patient with marked suppression of the sinus node is seen in Fig 7 The patient was a 23 year old man admitted to the hospital in deep coma because of a ruptured subarachnoid aneurysm There was no SA node activity and the AV junctional rate was 37/minute to 42/minute (Fig 7) Intermittent suppression of the AV junctional pacemaker occurred causing an idioventricular rhythm Administration of 1 5 mg of atropine restored a regular sinus rhythm

b Myocardial infarction During the past few years attitudes about the use of atropine for its effect on the heart rate in patients with acute myocardial infarction have been revised several times Atropine was recommended in acute myocardial infarction and sinus bradycardia because slow heart rate was associated with hypotension and increased ventricular irritability[15] and the beneficial effects of atropine on hypotension and ventricular arrhythmias were confirmed in the majority of clinical studies[15] In addition atropine was also used prophylactically to accelerate the heart rate in patients with bradycardia but without hypotension and ventricular irritability Use of the drug for bradycardia was suggested not

adverse effects in acute myocardial infarction initiated a series of investigations in which the arrhythmogenic effects of atropine were intensively studied, especially as mediated through the parasympathetic nervous system. That the autonomic nervous system is in a state of imbalance early in the acute stage of myocardial infarction was stressed by Webb and co-workers.[98] While some studies demonstrated that vagal stimulation increases the ventricular fibrillation threshold in dogs with acute myocardial infarction,[99] other studies suggest that the effect of the vagus on the ventricular fibrillation threshold can only be demonstrated on the normal myocardium and not on the ischemic myocardium.[100] Kolman and co-workers[101] believe that the beneficial effect of the vagus nerve in stabilizing ventricular irritability depends on the level of adrenergic activity, with vagal effects becoming apparent only if there is concomitant increased activity of its sympathetic counterpart.

Reviewing the adverse effect of atropine in acute myocardial infarction, we found that the only factor which was important in the pathogenesis of ventricular arrhythmias in man was the acceleration of the heart rate after atropine. An increased heart rate almost always preceded the appearance of increased ventricular irritability. The localization of the infarct, the age of the patient, or the time of administration of atropine did not seem to play an important role in the pathogenesis of ventricular arrhythmias after atropine, although tachycardia was more likely to appear after higher doses of atropine. This relationship is shown in the next illustrative case.

A 72-year-old patient was seen one hour after the onset of severe chest pain. The blood pressure was 70/50 mm Hg and the ECG showed marked sinus bradycardia (25/minute to 34/minute), first degree AV block and an acute inferior myocardial infarction (Fig. 9A). Administration of 0.5 mg of atropine did not influence the sinus rate. Following a second 0.5 mg dose of atropine the sinus rate accelerated to 130/minute (Fig. 9B). The sinus tachycardia was associated with increased ST segment elevation and was followed by ventricular tachycardia and ventricular fibrillation (Fig. 8C and D). Defibrillation was successfully carried out and the patient made a good recovery (Fig. 9E). This case demonstrated that atropine-induced ventricular irritability is preceded by acceleration of the sinus rate and supports the observation that at least 1.0 mg of atropine is necessary for the adverse effect of the drug.

Summary

The effects of atropine on various components of the specialized conduction system of the heart and the myocardium itself are reviewed. These actions are sometimes unpredictable or paradoxical, depending on the component showing the dominant effect and the health of the entire system. Atropine is best known for its chronotropic effect. Improved sinoatrial conduction has been demonstrated but the effect on the refractoriness of atrial muscle is unsettled. Atropine stimulates the atrioventricular (A-V) junctional pacemaker and facilitates conduction through the A-V node. The response of the subjunctional portion of the specialized conduction system to the drug is unpredictable and controversial in some respects.

Atropine is useful in the diagnosis of sinus node dysfunction, in the evaluation of coronary artery disease during atrial pacing, and in attempting to produce normal conduction in patients with the Wolff-Parkinson-White Syndrome. Its principal therapeutic application is in correcting the hypotension-bradycardia syndrome occurring during acute myocardial infarction. It also has a role in the temporary management of sinus node dysfunction. Atropine may also cause arrhythmias including atrial fibrillation, A-V dissociation, ventricular tachycardia, and ventricular fibrillation. The clinical settings in which atropine may be arrhythmogenic are discussed.

REFERENCES

81. Reiffel J A, Reid D S, and Bigger J T: Holte[r] monitoring and functional testing for sinus node dys[-] function (Abstract). Circulation 51 an[d] 52(Suppl)III 1975
82. Cokkinos D V, Katsaros S, Grivas, P, Bakoulas, G, and Plessas S T: Use of atropine for higher right atri[al] pacing rates. Maximal pacing for diagnosis of coronar[y] artery disease. Br Heart J 37:7?0, 19?3
83. Wolff L, Parkinson J, and White P D: Bundl[e] branch block with short PR interval in healthy youn[g] people prone to paroxysmal tachycardia. AM HEART J 5:685, 1930
84. Goldman I R, Cosby R S, and Griffith G C: Th[e] effect of atropine on the cardiac mechanism in anoma[-] lous atrioventricular conduction. AM HEART J 40:9?, 19?0
85. Wolff L, and Richman J L: The diagnosis of myocar[-] dial infarction in patients with anomalous atrioventric[-] ular excitation (W-P-W syndrome). AM HEART J 45:545, 1953

patients with myocardial infarction complicated by AV conduction disturbances is less certain Atropine may improve second and third degree AV block in patients with either inferior or anterior myocardial infarction [24, 96] but this effect on AV conduction is unpredictable We also believe that because of the variability of the response to atropine and the possible adverse effects of the drug a temporary pacemaker is the therapy of choice if the AV block causes hemodynamic deterioration or ventricular arrhythmias

IV Adverse effects of atropine

Until recently the adverse effects of atropine on the cardiac rhythm were thought to be infrequent and of little clinical significance Because atropine is now used more frequently than it was in the past we have become more aware of the implications of atropine induced complications In addition the drug is often administered to patients with acute myocardial infarction and unstable cardiac rhythm which is probably another cause of the higher incidence of adverse effects of atropine Most of the undesired effects of atropine are self limited and except for serious ventricular arrhythmias do not themselves require therapy The use of smaller doses of atropine in patients with acute myocardial infarction is probably the best way to avoid these complications

The adverse effects of atropine on the heart were extensively reviewed through 1970 by Scherf and Schott [97] Atrial fibrillation induced by vagolytic drugs was reported by Onnius in patients with acute myocardial infarction Supraventricular tachycardia after atropine was discussed earlier [65]

The occurrence of ventricular premature beats or ventricular tachycardia after administration of atropine in patients without cardiac disease is rare Dauchot and Gravenstein [99] who studied the effect of atropine on the cardiac rhythm in 79 patients showed that the drug caused ventricular premature beats in one older patient On the other hand simultaneous administration of atropine with halothane and cyclopropane which are myocardial depressants may lead to serious ventricular arrhythmias even in patients without heart disease

The following case shows a possible pseudo adverse effect of atropine A His bundle recording from a 68 year old woman with a history of

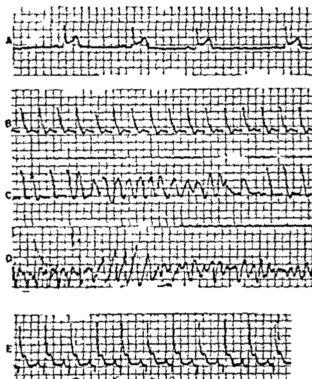


Fig 9 (Patient 8) Atropine-induced ventricular fibrillation in a patient with acute inferior myocardial infarction *A* lead II shows sinus bradycardia (25-34/min.) PR interval of 0.2 second and ST segment elevation *B* following the administration of 1 0 mg of atropine the sinus rate accelerates to 130/min This is associated with an increase in the ST segment elevation. *C D* ventricular tachycardia and ventricular fibrillation then appear *E* sinus rhythm is restored by defibrillation.

syncope is shown in Fig 8 The ECG revealed sinus rhythm frequent atrial premature beats some blocked and others with aberrant ventricular conduction His bundle recording confirmed the blocked atrial premature beats which were the cause of the bradycardia (Fig 8*A*) Administration of 0 5 mg of atropine did not abolish the atrial premature beats but improved the AV conduction so that all the atrial premature beats were now aberrantly conducted (Fig 8*B*) Blocked atrial premature beats are readily recognized on 12 lead ECG s because the atrial deflection can be identified at least in some of the leads However if only a single monitor lead is analyzed as is usually done in the CCU the identification and diagnosis of nonconducted APC s may be difficult Had this patient been monitored with a single lead the appearance of APC s after atropine might have been erroneously interpreted as an adverse effect of the drug

The wide use of atropine and its potential

Of right ventricular congestive heart failure

Selected pathophysiologic aspects of left ventricular congestive heart failure were discussed previously but right ventricular congestive heart failure (RVCHF) was not considered in detail in these discussions The same general arguments that apply to the left ventricle (LV) the left pump of the heart also apply to the right ventricle (RV) the right pump of the heart However there are specific differences For example there are essentially 500 c c of blood in the pulmonary blood vessels and 4,500 c c in the systemic blood vessels when the heart is normal and fully compensated and each ventricle is pumping the same volume of blood and the two pumps are well synchronized For illustrative purposes if it is assumed that each ventricle pumps 100 c c per stroke and the heart rate is 100 beats per minute and if all things remained equal the volume of blood in the pulmonary and systemic circulations would remain stabilized as indicated i e 500 and 4,500 c c respectively for the pulmonary and systemic vascular systems. However if the right ventricle were to fail slightly and pump 99 c c of blood per stroke while the left ventricle continued to pump 100 c c per stroke each minute 100 c c of blood would be removed from the pulmonary circulation and pumped into the systemic circulation. The pulmonary circulation would become relatively empty or dry " and the volume of blood in the systemic circulation would increase—a volume increase which the systemic veins could readily accommodate provided they are not "tightened by sympathetic nervous system activity But regardless of how small the total pulmonary blood volume becomes the volume of blood within the pulmonary vessels is always equal to the volume of the lumina of the pulmonary vessels thus the pulmonary vessels, especially the pulmonary veins would become relatively loose as the hoop tension of the wall reduced unless the tone of the smooth muscles in the walls of the vessels actively increased by means of autonomic nervous system activity If all of the blood from the lungs (500 c c) was displaced into the systemic circulation, the systemic circulation could readily accommodate the 500 c c just as it so readily accommodates a 500 c c blood transfusion

But as is well known clinically with right ventricular congestive heart failure (RVCHF) the neck veins become distended and the patient develops systemic venous hypertension edema ascites pericardial and pleural effusion etc Why do these pathophysiologic manifestations occur? The abnormal non-synchronized state of the two pumps (RV and LV) results in the clinical state of RVCHF with the increase in tone (constriction) of the systemic veins as described previously Why and by what mechanism this increase in α and β-adrenergic sympathetic tone of the systemic blood vessels occurs are not known [illegible] clinical and physiologic data indicate that this increase in sympathetic tone or activity does occur The mechanisms by which water and electrolytes are subsequently retained are also not known. The water and electrolyte retaining pathologic mechanisms must be related in large part to alteration in renal function (not renal disease), as noted before resulting from dysfunction of the two cardiac pumps The increase in sympathetic tone could initiate physiologic phenomena which could produce the well known renal dysfunction of CHF responsible for the accumulation of edema fluid.

Surely in less than 5 minutes the left ventricular stroke volume would have to decrease to the stroke volume of the RV but the volume of blood in the pulmonary circulation could remain reduced It could slowly return to normal levels by means of readjustments in the stroke volume of the two ventricles and readjustments of the vascular renal, autonomic nervous system dysfunction, etc But if the original factor which caused the RV to reduce its stroke volume in the first place were still present one can only wonder if the sympathetic (α and β) tone would return to normal even if the volume of blood in the pulmonary vessels returned to the normal level of 500 c c

This discussion of CHF illustrates again what great difference in the state of circulation could be produced by only 1 c.c. stroke volume difference between the two cardiac pumps. One can readily calculate the rates of change in the circulation that could be produced by any reasonable differences in stroke volume for the two pumps and at different heart rates.

Furthermore is there such a *clinical* state as RVCHF with a normal LV function i.e RVCHF without LVCHF? Theoretically it could exist with "pure or strict pulmonary stenosis, such as with a congenital defect or in cor pulmonale

G E Burch MD
Tulane University School of Medicine and Charity Hospital of Louisiana New Orleans La

REFERENCES

1 Burch, G E A Primer of Congestive Heart Failure Springfield 1954 Charles C Thomas Publisher
2 Burch, G E Congestive heart failure is not due to low cardiac output *per se* AM HEART J 94 269 1977
3 Burch, G E Of why the two heart pumps are anatomically united to form one heart AM HEART J 95 811 1978
4 Burch, G E The role of the central nervous system in chronic congestive heart failure AM HEART J 95 255 1978

0002-8703/80/080262 + 01$00 10/0

© 1980 The C V Mosby Co

86 Averill, K. H., Fosmoe R J., and Lamb L. E Electrocardiographic findings in 67,375 asymptomatic subjects Wolff Parkinson White syndrome Am J Cardiol. 6 108 1960
87 Kent K M Smith, E R., Redwood D R., and Epstein S E Electrical stability of acutely ischemic myocardium. Influence of the heart rate and vagal stimulation Circulation 47 291 1973
88 Epstein S E Goldstein R E., Redwood D R Kent K. M and Smith, E R. The early phase of acute myocardial infarction Pharmacologic aspects of therapy Ann Intern Med 78 918 1973
89 Massumi, R. A., Mason D T., Amsterdam, E A., deMaria, A Miller R R., Scheinman M and Zelis, R Ventricular fibrillation and tachycardia after intravenous atropine for treatment of bradycardias N Engl J Med 287 336 1972
90 Zipes D P., Knoebel, S B Rapid rate-dependent ventricular ectopy Adverse responses to atropine induced rate increases, Chest 62 255 1972
91 Richman S Adverse effect of atropine during myocardial infarction Enhancement of ischemia following intravenously administered atropine J A M A 228 1414 1974
92 Redwood, K R., Smith E R., Epstein S E Coronary artery occlusion in the conscious dog Effect of alteration in the heart rate and arterial pressure on the decrease of myocardial ischemia Circulation 46 323 1973
93 Miller R. R., Olson H. G., Vera Z. deMaria A N Amsterdam E. A., and Mason D T Clinical evaluation of the enhancement of vagal tone in acute myocardial infarction by edrophonium hydrochloride Effects on ventricular arrhythmias, His bundle electrography and left ventricular function AM HEART J 93 7?? 1977
94 Shell, W E., Sobel B E Deleterious effects of increased heart rate on infarct size in the conscious dog Am. J Cardiol 31 474 1973
95 Atropine after myocardial infarction (Editorial) Lancet 2 1183 1972
96 Pantridge J F., Adgey A. A J., Geddes, J S., Webb Sw The acute coronary attack, New York, 1975 Grune & Stratton, Inc. p 46
97 Scherf D., Schott A. Extrasystoles and Allied Arrhythmias, Chicago 1973 Year Book Medical Publishers, pp 741 745
98 Onnius, E Arrhythmias after treatment with parasympatholytic drugs, in Symposium on Cardiac Arrhythmias, edited by Sandoe E., Flensted-Jensen E., and Olesen K H., Sodertalje Sweden, 1970 AB Astra pp 559-563
99 Dauchot P., and Gravenstein J S Effects of atropine on the electrocardiogram in different age groups, Clin Pharmacol Ther 21 274 1971
100 Yoon, M S Han J Tse W W., and Rogers, R. Effects of vagal stimulation, atropine and propranolol on fibrillation threshold of normal and ischemic ventricle AM HEART J 93 60 1977
101 Kolman, B S., Verner R L., and Lown, B., The effect of vagus nerve stimulation upon vulnerability of the canine ventricle role of sympathetic parasympathetic interaction Circulation 52 5 8 1975
102 Hoffman B F The genesis of cardiac arrhythmias, Progr Cardiovasc Dis 8 319 1966
103 Scherlag B J Hope R R., Williams, D O., El-Sherif N and Lazzara R. Mechanism of ectopic rhythm formation due to myocardial ischemia Effects of heart rate and ventricular premature beats, in Wellens, H J J Lie K I Janse M J., eds., The conduction system of the heart. Structure function and clinical implication, Philadelphia 19 6, Lea & Febiger pp 633-649
104 Merx, W., Yoon M. S and Han J The role of local disparity in conduction and recovery time on ventricular vulnerability to fibrillation AM HEART J 94 603 1977
105 Chadda K D., Banka V S and Helfant, R H Rate dependent ventricular ectopia following acute coronary occlusion. The concept of an optimal antiarrhythmic heart rate Circulation 49 654 1974

IMPORTANT
INFORMATION FOR AUTHORS

Effective June 1 1980 all manuscripts for the AMERICAN HEART JOURNAL should be sent to

Dean T Mason M D
Section of Cardiovascular Medicine
University of California
School of Medicine
Davis California 95616

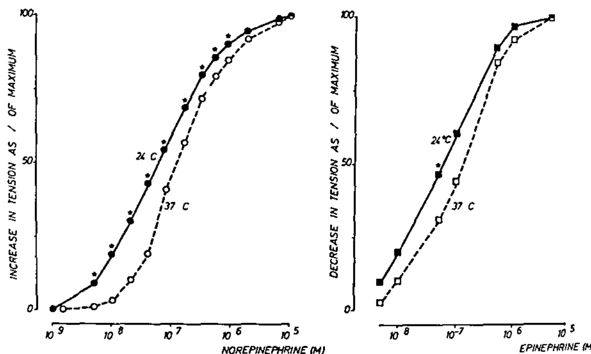


Fig 2 Demonstration that in cutaneous vessels moderate cooling augments the responsiveness of the vascular smooth muscle cells to both the alpha and beta adrenergic effects of catecholamines The experiments were performed on isolated rings of canine saphenous veins *Left* the rings were made to contract with increasing concentrations of norepinephrine throughout the experiment neuronal disposition of norepinephrine as well as beta adrenergic receptors are blocked by the appropriate pharmacological agents Cooling from 37 (o--o) to 24 C (●—●) shifts the dose response curve to norepinephrine to the left the maximal contractile answers to the catecholamine were not significantly different at both temperatures (Data from Ref 9) Potentiation by local cooling is also obtained during sympathetic nerve stimulation *Right* the rings were first made to contract with acetylcholine in the presence of phentolamine to block alpha adrenergic receptors the relaxation caused by increasing concentrations of epinephrine was then investigated at 37° (□ -□) and 24 C (■—■) Cooling markedly facilitates the inhibitory effect of epinephrine Similar augmentation by moderate cooling of the beta adrenergic responsiveness has been described for isoproterenol and norepinephrine * = value at 24 C significantly different from that at 37 C ($P < 0.05$ Student s t test)

ents the arterial and venous responses to sympathetic nerve ctivation The enhanced arteriolar constriction limits the mount of blood flowing through the skin The augmented enoconstriction directs the venous return to the deep venae omitantes which run alongside the deep arteries Unlike itaneous vessels deep vessels dilate when they are exposed to ie colder blood coming from the skin This favors the counter-current exchange of heat which warms up the enous blood returning to the body core The augmented esponse of cutaneous blood vessels to sympathetic nerve ctivity during moderate cooling is due to two factors (Fig 1) irst lowering the temperature delays the disappearance of ie adrenergic neurotransmitter from the junctional cleft etween the adrenergi nerve endings and the cutaneous ascular smooth muscle because it inhibits neuronal uptake nzymatic degradation and diffu ion of norepinephrine hus, the amount of transmitter in the icinity of the alpha drenergic receptors of the va ular effector cells increases urther moderate cooling greatly augments the respon ive ess of the cutaneous vascular m ooth muscle to norepineph ine (Fig 2 *left*) because the affinity of their alpha adrenergic receptors significantly increases this increase in affinity holds not only for norepinephrine but also for alpha adrenergic antagonists At the same time moderate cooling augments the sensitivity of the vascular smooth muscle for the beta adrenergic effects of catecholamines which in normal conditions presumably tempers the increased responsiveness to the alpha adrenergic effect of these substances (Fig 2, *right*)

It is tempting to assume that in primary Raynaud s disease the vasospasm associated with exposure to cold involves the local potentiating effect that temperature has on the cutaneous vasomotor response to sympathetic nerve activation, and in many instances is only an exacerbation of the physiological mechanism The importance of the autonomic nervous system in providing the initiating signal for vasoconstriction is illustrated by the observations that the onset of the symptoms is frequently related to situations where emotional stress augments the sympathetic outflow to the cutaneous vessels, and that reserpine or sympathectomy may alleviate the symptoms ' However the abnormality is primarily a dysfunction of the vascular smooth muscle cells, since epi

Thermosensitivity of cutaneous vessels and Raynaud's disease*

Raynaud s disease is characterized by prolonged pasm of the digital arteries of the hand when they are exposed to a cold stimulus particularly when the subjects are emotionally upset The exact mechanism underlying the vasospasm is unknown

Thermoregulatory needs are the main determinants of cutaneous blood flow Hence the sympathetic outflow to the cutaneous arterioles arteriovenous anastomoses and veins is continuously adjusted by the hypothalamic thermoregulatory centers. When the body temperature increases the sympathetic outflow to the skin blood vessels decreases and the weat glands are activated and produce kinins as a result the arterioles, the arteriovenous anastomoses, and the veins open Large amounts of blood are shunted to the latter which act as a capacious radiator for the physical exchange of heat When the body temperature decreases, the sympathetic outflow to the skin is augmented, sweat secretion is inhibited and the dissipation of heat is restricted Besides thermoregulatory adaptations, the skin vessels participate in homeostatic reflexes and in the cardiovascular response to emotional stress

Local cooling (from 37 C to about 15 C) greatly aug

*Presented at the meeting of the Belgian Angiological Society on January 13, 1979

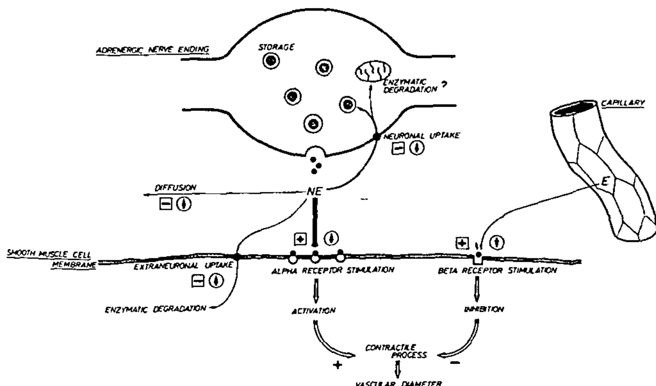


Fig 1 When the sympathetic nerves are active cooling affects both the adrenergic nerve ending and the vascular smooth muscle cell in cutaneous vessels The release of norepinephrine from the adrenergic nerve ending is most likely not affected by moderate cooling Neuronal uptake and enzymatic degradation of norepinephrine are depressed by moderate cooling as well as by diffusion of the neurotransmitter out of the junctional cleft This partially explains the increased constriction upon cooling in densely innervated cutaneous vessels since the concentration of the adrenergic neurotransmitter increases in the vicinity of the effector cells. In addition more norepinephrine binds to the alpha adrenergic receptor sites at lower temperatures leading to greater activation of the contractile process and thus to increased constriction of these vessels. The potentiating effect of cold is partly offset by the facilitation of the beta adrenergic effects of the catecholamines NE = norepinephrine E = epinephrine □ = effect of temperature O = contractile response ↑ = augmentation ↓ = depression

0002-8703/80/080263 + 03$00.30/0 © 1980 The C V Mosby Co

disturbances in blood flow may be responsible for clinical manifestations in BMLS and the condition has been called an ischemic cardiomyopathy at the Montreal Heart Institute [2] on account of an unduly large LV mass in relation to coronary blood flow

These abnormal findings have not always been confirmed when other investigators have applied the same tests to their groups of MLP patients [2] However it is very difficult in this situation where the index entity is common and the clinical spectrum wide to be sure that studies with disparate results have compared like with like Measurement of LV function in the intact human heart is problematical and the frequent coexistence of mitral regurgitation and LV wall motion abnormalities in patients with MLP coming to catheter study [4] adds to the methodological difficulties A drawback of thallium imaging of myocardial perfusion is its rather poor resolution a particularly unfortunate feature when the supposed abnormalities must lie in the small arteries beyond the resolution of standard contrast cineangiography Moreover myocardial uptake of thallium is not purely flow-dependent and if as Selwyn and associates have stated regional disturbances in myocardial perfusion can be identified with this indicator only when metabolic abnormalities affecting cellular uptake are present it follows that those MLP patients with stress scintigraphy defects have disturbed myocardial cellular metabolism Thus it is prudent to consider the extant reports of myocardial dysfunction and perfusion abnormalities in BMLS with realistic caution

Opportunities for direct examination of myocardial tissue obtained at necropsy from subjects with BMLS are not common and no distinctive abnormality has been recognized [2] Only recently have techniques of biopsy during cardiac catheterization made it possible to obtain endomyocardial tissue samples safely during life and it is of great interest that the two studies so far published have both presented evidence of myocardial abnormality in BMLS The report from Stanford done in 1978 is of right ventricular biopsy by a technique refined in cardiac transplantation follow up studies and carried out in 14 patients with BMLS Light microscopy revealed an increase in endocardial and interstitial fibrosis in eight cases Electron microscopy in 11 cases showed mitochondrial degenerative changes usually marked or severe in all and definite myocyte degeneration in four Nuclear chromatin clumping and intracell edema were more prominent in BMLS biopsies than in control specimens obtained at transplantation from 10 normal donor hearts The inevitable criticism of this important study is that the tissue from the right side of the interventricular septum may not be representative of the myocardium beneath the prolapsing mitral valve

Left ventricular tissue is accessible for percutaneous transarterial biopsy and a method by which a bioptome can speedily and repeatedly be passed via a Teflon long sheath to obtain multiple endomyocardial biopsies has been described in detail With experience in developing this technique and an established laboratory dedicated to the analysis of biopsy specimens obtained during open heart surgery we were able at St Thomas Hospital London to address in a direct and novel fashion the question of ar normality of the LV in BMLS patients undergoing cardiac catheterization Endomyocardial LV biopsies from 11 patients wi h 1LP distressing chest pain little or no mitral regurgitati and normal coronary arteries were examined by cellular chemical and biophysical methods [1] Comparison was made with biopsies from a good LV" control group in which normal LV function was judged by seven or eight indices and from a bad LV' control group in which these indices were markedly abnormal Histochemical findings in the MLP biopsies ranged from normal to very abnormal and on a semiquantitative rating of over all histochemical abnormality the MLP group were significantly worse ($p < 0\,001$) than the good LV controls and also worse than the bad LV controls but not significantly so The results for monoamine oxidase (MAO) activity reflecting ability of myofibrils to metabolize catecholamines were particularly poor with eight of the 11 MLP specimens showing abnormal MAO activity compared with 11 of 21 in the bad LV and only two of eight in the good LV group The ability of muscle fibers in unfixed biopsy sections to respond to the standardized stimulus of adenosine triphosphate (ATP) plus ionic calcium was measured in terms of alteration in birefringence of the myofibrils believed to be brought about by ATP mediated orientation of myosin micelles [a] The birefringence response to ATP was markedly impaired in tissue from MLP patients with the group results in a position between the good LV and bad LV controls and significantly different from both The clear distinction ($p < 0\,005$) between the good LV controls and the MLP group suggests a distinct abnormality of muscle function in the latter for this birefringence method has been shown capable of registering myocardial deterioration during cardiopulmonary bypass. Such evidence of abnormal muscle function in this subgroup of patients with MLP and chest pain is of particular importance because it has been obtained by a method independent of the problems of assessing myocardial function in the intact ventricle

The myocardial biopsy evidence from Stanford and London [7] strongly supports the concept of a diffuse abnormality of the myocardium in those patients with BMLS in whom symptoms have been sufficiently prominent to warrant cardiac catheterization It is difficult to refute use of the term cardiomyopathy in this situation Because of the major role of catecholamines in myocardial contraction the MAO abnormalities could well be part of the fundamental defect responsible for impairment of the birefringence response to ATP in the specimens from MLP patients The beta adrenergic blocking drug propranolol has acquired a reputation for usefulness in treating chest pain and other symptoms in BMLS and there may be some link between the histochemically demonstrable MAO abnormalities and this clinical impression No theory to explain the chest pain of BMLS has yet gained general acceptance [2] but the cellular abnormalities to which the biopsy data now testify surely point to a metabolic/ biochemical mechanism as the most likely explanation. Further investigation of the pathophysiology and treatment of BMLS are now indicated and will be particularly welcomed by those in clinical practice who struggle with the management of patients with severe non anginal chest pain and without any demonstrable cardiac abnormality except MLP

Alasdair D Malcolm M.Sc M R C P (U K) F R C.P.(C)
Consultant Physician
Airedale General Ho pital
Steeton Nr Keighley
West Yorkshire BD20 6TD
England

sodes of vasospasm still can be induced by exposure of the fingers to cold after sympathectomy In patients where the phenomenon is primarily due to hypersensitivity of the alpha adrenoceptors to the sensitizing action of cooling, ther apeutical effects are obtained with alpha adrenergic blocking agents it is to be expected from the studies on isolated blood vessels that the vessels exposed to the cold will be particular ly susceptible to alpha adrenergic blockade and thus that doses of blocking agents may be used which have little effect on general hemodynamics. Raynaud s disease sometimes is uccessfully treated with beta receptor stimulating agents. Treatment with beta adrenergic blocking agents induces Ray naud s phenomenon Raynaud s disease is relatively fre quent in patients suffering from hypothyroidism In the animal, beta adrenergic sensitivity decreases with a e a process which can be reversed by administration of thyroid hormone These different observations all imply that Ray naud s disease could be due to a relative lack of beta adrenergic sensitivity of the cutaneous vessels This then would exaggerate the augmentation by local cooling of the vasoconstri tor response of these vessels to the alpha adrener gic effect of the catecholamines

P M Vanhoutte M D
W J Janssens B Sc
Universitaire Instelling
Antwerpen Wilrijk Belgium

REFERENCES

1 Shepherd, J T Physiology of the Circulation in Human Limbs in Health and Disease Philadelphia 1963 W B Saunders Company
2 Shepherd J T and Vanhoutte P M The human cardiovascular system Facts and concepts, New York 1980 Raven Press
3 Vanhoutte P M and Shepherd J T Effect of temperature on reactivity of isolated cutaneous veins of the dog Am J Physiol. 218 187 1970
4 Vanhoutte P M and Lorenz R R Effect of temperature on the reactivity of saphenous mesenteric and femoral veins of the dog Am J Physiol 218 1746 1970
5 Shepherd, J T and Vanhoutte P M Veins and their Control, London Philadelphia 1975 W.B Saunders Company
6 Vanhoutte P M Physical factors and regulation of vascular smooth muscle function *in* Handbook of Physiology Vascular Smooth Muscle ed by D.F Bohr A.P Somlyo and H V Sparks, Bethesda Md., 1980 The American Physiological Society
7 Janssens, W J., and Vanhoutte P M Effect of cooling on COMT activity in canine saphenous vein homogenates determined by a micro-radioenzymatic assay Arch. Int Pharmacodyn 236 305 1978
8 Janssens, W J and Vanhoutte P M Effect of cooling on efflux of H norepinephrine in canine cutaneous vein Br J Pharmacol 66 148P 1979
9 Janssens, W J and Vanhoutte P M Instantaneous changes of alpha-adrenoceptor affinity caused by moderate cooling in canine cutaneous veins, Am. J Physiol 234 H330 1978
10 Vanhoutte P M and Shepherd J T Effect of cooling on beta receptor mechanisms in isolated cutaneous veins of the dog Microvasc Res. 2 454 1970
11 Peacock, J H Primary Raynaud disease observations on its etiology and treatment British Surgical Practice Surgical Progress London 1960 Butterworths, p 2
12 Tindall J P Whalen R E., and Burton E E Medical uses of intra arterial injections of reserpine treatment of Raynaud syndrome and of some vascular insufficiencies of the lower extremities Arch. Dermatol 110 233 1974
13 Lewis T and Pickering G W Observations upon maladies in which blood supply to the digits ceases intermittently or permanently and upon bilateral gangrene of digits. Observations relevant to so-called Raynaud s disease Clin Sci. 1 327 1934
14 Thune P and Fyrand O Further observations on the therapy with a beta stimulating agent in Raynaud s phenomenon, Acta Chir Scand Suppl 465 94 1976
15 Marshall, A J Roberts, C J C and Barritt D W Raynaud s phenomenon as side effect of beta blockers in hypertension Br Med. J 1 1498 1976
16 Thulesius, O Primary and secondary Raynaud phenomena Acta Chir Scand Suppl. 465 5 1976
17 Berkowitz B Vascular relaxation and aging *in* Mechanisms of Vasodilatation ed by P M Vanhoutte and I Leusen Basel 1978 S Karger p 173

Myocardial mysteries surrounding mitral leaflet prolapse

Excessive bulging of one or both leaflets of the mitral valve has proved to be a remarkably common disorder but the hearts of subjects with such valves have not readily yielded up their secrets. Certain symptoms notably chest pain and palpitation mysteriously associated with mitral leaflet prolapse (MLP) have prompted investigation of the state of the left ventricle (LV) as well as the mitral valve itself in the symptomatic primary form of the disorder designated billowing mitral leaflet syndrome (BMLS) by Barlow and Pocock in their recent Editorial in this JOURNAL

Suggestive evidence of a myocardial abnormality in patients with MLP has been obtained by a variety of means Crude indications of LV dysfunction in terms of elevated resting LV end-diastolic pressure (LVEDP) an abnormal rise in LVEDP and/or cardiac index on exercise or a failure to lower LVEDP appropriately in response to atrial pacing, have been reported Abnormal myocardial lactate metabolism has been documented in four studies Reports from Toronto and Milwaukee of ²⁰¹ thallium myocardial perfusion imaging defects on stress testing have fostered speculation that local

0002-8703/80/080265 + 03$00.30/0 © 1980 The C V Mosby Co

Table I Effects of venesection on hematocrit blood viscosity and general blood flow in chronic lung disease

	Normal	*Before venesection*	*After venesection*	*P*
Hematocrit (%)	43 3 ± 7 1	59 6 ± 6 8	43 9 ± 2 2	< 0 005
Viscosity (CPS)	4 06 ± 0 36	5 83 ± 0 46	3 80 ± 0 25	< 0 005
Supratentorial CBF†		32 2 ± 5 2	57.3 ± 14 6	< 0 005
Subtentorial CBF†		50 7 ± 11 0	63 8 ± 31 4	N.S
Hemispherical mean CBF†		38 3 ± 5 1	60.2 ± 20 1	< 0 025

Values expressed as mean ± SD
Blood viscosity obtained at shear rate 225 sec (Centipoise)
†Cerebral blood flow (CBF) units are expressed as mL/100 g /min
N S = refers to non-significant p value greater than 0 05

cell production increases relatively linearly with decreases in hemoglobin oxygen saturation

However in patients with lung disease where arterial carbon dioxide tension may be abnormal leading to respiratory acidosis or alkalosis there is a less well defined relationship between the degree of hemoglobin unsaturation and the red cell mass than is characteristically seen in normal subjects at altitude It has been suggested that patients with chronic lung disease have an attenuated bone marrow response or that red cells have a decreased life span which could contribute to the variable red cell mass in lung patients compared to normals at altitude Another factor which could result in a lower red cell mass for a given degree of arterial unsaturation is the increased cardiac output seen in some patients with chronic lung disease With a higher cardiac output the delivery of oxygen to various tissues is increased and if intrarenal oxygen sensors responsible for the erythropoietin response were exposed to a normal oxygen supply then it is understandable why some patients would not have secondary polycythemia in spite of decreased arterial blood oxygen saturation

Although increased red cell mass improves the oxygen carrying capacity of blood it also increases blood viscosity which tends to impede blood flow Since blood with its particulate matter is not a Newtonian fluid its viscosity increases with increases in red cell concentration The shape of individual red cells also affects viscosity and shape changes leading to elevated viscosity occur in hypoxic and hypercapnic blood Because of differing metabolic rates in individual tissues blood viscosity could be quite different in individual vascular beds. Also viscosity is affected by vascular geometry and by the rate of blood flow Controlled changes in hematocrit and blood viscosity have been shown to affect the resistance to flow in the pulmonary[a] and peripheral circulations The clinical significance of increased viscosity on pulmonary vascular resistance is controversial since both improvement in and no significant change in pulmonary vascular resistance have been reported following a reduction in hematocrit by venesection

The clinical management of secondary polycythemia is not generally agreed upon Although symptomatic improvement in mental acuity vitality and breathing ability has been volunteered by patients whose polycythemia was treated by venesection objective data on the mechanisms producing these symptomatic changes are s[illegible]se Venesection does not alter measured pulmonary function although work capac ity has been demonstrated to improve

The most direct way of reducing red cell mass is by venesection It reduces both the red cell mass and the blood volume in cardiac failure due to cor pulmonale and it has been advocated as a preventive measure a ainst the recur rence of cardiac failure after compensation A consensus of opinion has arisen that venesection is of doubtful value expect to reduce the incidence of thrombotic complications noted when the red cell mass is increased

We measured cerebral blood flow with xenon 133 before and after venesection in six chronic hypoxic pulmonary diseas patients with polycythemia We demonstrated that venesec tion increased cerebral flow and that the increase appeared to be preferentially greater to the cerebral cortex (Table I) We did not correct the cerebral blood flow values in Table I fo changes in partition coefficient resulting from changes i hemoglobin concentration because there is uncertainty abou the actual tissue blood xenon 133 partition coefficient in th living brain It is known that this coefficient increases wit decreases in hemoglobin concentration and use of the correc tion factor would result in our measured prevenesectio cerebral blood flow values being lower than those shown Therefore venesection to correct secondary polycythemia ma actually result in a larger increase in cerebral blood flow tha that reported in Table I

The improved flow to the cerebrum could explain th symptomatic improvement noted by these patients sinc neither mechanical lung function blood gas values or pulmo nary artery pressure (as judged from the distribution o pulmonary blood flow) changed significantly in them

Venesection has been shown to increase cerebral blood flo in patients suffering from primary polycythemia with o without cerebrovascular accidents Cerebral blood flow ha also been demonstrated to increase in association with th general improvement noted on recovery from ruptured cer bral aneurysms It would appear that optimal blood flo occurs at a physiological hematocrit of 45%

A less direct approach to achieve a lower hematocrit and t reduce pulmonary artery pressure is by adminis ration o continuous oxygen which has been found to be clinicall beneficial in patients with polycythemia secondary to hypo emia There is a reduction in hematocrit in about 6 weeks an a decreased incidence of hospitalization due to cor pulmon ale[20] In patients with severe hypoxemia this therapeut

REFERENCES

1 Barlow J B and Pocock, W A Mitral valve prolapse the specific billowing mitral leaflet syndrome or an insignificant non-ejection systolic click AM HEART J 97:?77 19 9
2 Jeresaty R M Mitral Valve Prolapse New York 1979 Raven Press
3 Gulotta S J Gulco L Padmanabhan V and Miller S The syndrome of systolic click murmur and mitral valve prolapse—a cardiomyopathy? Circulation 49 717 19,4
4 Malcolm, A D Boughner D R, Kostuk W J and Ahuja S P Clinical features and investigative findings in presence of mitral leaflet prolapse Study of 85 consecutive patients Br Heart J 38 244 19 6
5 Natarajan G Nakhjavan F K, Kahn D Yazdanfar S Sahibzada W Khawaja F, and Goldberg H Myocardial metabolic studies in prolapsing mitral leaflet syndrome Circulation 52 1105 1975
6 Feitosa G S Bentivoglio L G Urricchio J F Meister S G and Frankl W S Left ventricular end diastolic pressure response to atrial pacing in idiopathic mitral valve prolapse Clin Cardiol 1 80 19 8
7 Koch, F H Billingham M E Mason J W Cipriano P R and Hancock W Pathogenesis of the click murmur prolapse syndrome Biopsy evidence supporting an underlying cardiomyopathic process (Abst) Am J Cardiol. 39 272 1977
8 Duca P R Gottlieb R Kasparian H Weiner L Brest A N Ruggerio N and Scaniato A Abnormal myocardial lactate metabolism as an additional feature of the syndrome of mitral valve prolapse (Abst) Am J Cardiol 35 133 1975
9 Khullar S C and Leighton R F Myocardial lactate production in mitral valve prolapse syndrome (Abst) Circulation 49 and 50 (Suppl III) 232 1974
10 McLaughlin, P Huckell V Staniloff H Buda A Feiglin D, Wigle D and Morch J Exercise induced chest pain myocardial perfusion and stress electrocardiography in patients with mitral valve prolapse (Abst) Circulation 55 and 56 (Suppl III) 216 1977
11 Tresch, D D Soin J S Siegel, R Love M and Keelan M H Jr Mitral valve prolapse—evidence for a myocardial perfusion abnormality (Abst) Am J Cardiol. 41 441 1978
12 Pasternac A Streulens Y Gervais A Noble J and Bourassa M G The systolic click syndrome an "ischemic cardiomyopathy"? (Abst) Am J Cardiol. 37 161 19 6
13 Mirsky I Pasternac A Ellison R C, and Hugenholtz P G Clinical application of force-velocity parameters and the concept of a normalized velocity" in Cardiac Mechanics Physiological Clinical and Mathematical Considerations edited by I Mirsky D N Ghista and H Sandler New York 1974 John Wiley & Sons, Inc pp 293-329
14 Koletti, M Jenkins B S and Webb Peploe M M Assessment of left ventricular function by indices derived from aortic flow velocity Br Heart J 38 18 1976
15 Selwyn A P Fox K and Shillingford J P Myocardial imaging with extractable cations and inert tracers the effects of flow and metabolism Clin. Cardiol 1 60 1978
16 Mason J W Koch F H Billingham M E and Winkle R A Cardiac biopsy evidence for a cardiomyopathy associated with symptomatic mitral valve prolapse Am J Cardiol 42 557 1978
17 Malcolm A D Čanković Darracott S Chayen J, Jenkins B S and Webb Peploe M M Biopsy evidence of left ventricular myocardial abnormality in patients with mitral leaflet prolapse and chest pain Lancet 1 10?? 1979
18 Brooksby I A B Jenkins B S Davies, M J Swanton R H Coltart D J and Webb Peploe M M Left ventricular endomyocardial biopsy 1 description and evaluation of the technique Cathet Cardiovasc Diagn. 3 115 1977
19 Čanković Darracott, S Braimbridge M V Williams, B T Bitensky L and Chayen J Myocardial preservation during aortic valve surgery assessment of five techniques by cellular chemical and biophysical methods J Thorac Cardiovasc Surg 73 699 1977
20 Braimbridge M V, and Čanković Darracott, S Quantitative polarization microscopy and cytochemistry in assessing myocardial function in Quantitative Cytochemistry and its Applications edited by J R Patterson L Bitensky and J Chayen, London 1979 Academic Press pp 221 230

Management of secondary polycythemia with hypoxic lung disease*

Although hypoxemia resulting from chronic lung disease is a common medical condition it is relatively uncommon to see polycythemia associated with these lung disorders The polycythemia secondary to hypoxemia is mediated by increased erythropoietin production but erythropoietin levels and therefore red cell mass can also be increased in the presence of certain tumors and renal disorders.

The increase in red cell mass is a beneficial physiological adjustment to hypoxemia since more oxygen can be carried in each milliliter of blood for a given arterial oxygen tension Because of the shape of the oxygen dissociation curve there is not a dramatic decrease in the oxygen saturation of hemoglobin and therefore oxygen content of blood until oxygen tension falls below about 65 mm Hg It is interesting that red

*Supported by a Grant from the Alberta Thoracic Society and in part by the Medical Services Research Foundation of Alberta Canada

000? 8 03/80/080?67 + 03$00 30/0 © 1980 The C V Mosby Co

Toxic polyneuritis and toxic hepatitis related to long term perhexiline maleate therapy

To the Editor

In the article Assessment of perhexiline maleate in angiographically proven intractable angina by M Afzal Mir (AM HEART J 96 350 1978) some side effects of the drug are reported such as tremor dizziness nausea though not severe enough to impair the general condition of the patient However in a few cases serious side effects have been observed indicating liver and nervous system damage with anatomical toxic hepatitis segmentary demyelination of the peripheral nerves and decreasing of proprioceptive reflexes pallesthetic deficit and visual impairment

We have recently observed extremely severe liver and peripheral nerve impairment in a 51 year old male patient who had been taking perhexiline maleate (PM) at the following dosages 600 mg daily for 1 month 400 mg daily for the next 3 months and 200 mg daily for a further 16 months

Symptoms of peripheral neuropathy appeared during the last 3 months of treatment namely peripheral tingling of the four limbs weakness of the four limb muscles (mainly of the legs) impairment of the flexion and extension movements of the feet of the flexion and abduction movements of the thigh and impairment of the fine movements of the fingers with muscular hypotrophy Furthermore he was complaining of headache dizziness waddling gait with pallesthetic deficit visual impairment and bilateral papilledema The physical examination demonstrated a large and hard liver with an edge 4 cm below the costal margin (not previously observed) and physical findings of peripheral neuropathy The SGOT was 100 I U SGPT was 60 I U and alkaline phosphatase 5 I U

On electromyogram (EMG) examination a slight reduction of motor unit recruitment on voluntary contraction was observed in the extensor muscles of the forearms and in the small muscles of the hands In the lower limbs a moderate motor unit reduction was observed distally more evident in the muscles of the anterior compartment of the legs Motor conduction studies performed in ulnar median deep peroneal and posterior tibial nerves showed a severe slowing with a marked time scattering of the motor responses These findings were in agreement with a peripheral neuropathy in which segmental demyelination was likely to be the main feature The conduction velocity of peripheral sensorial and motor nerves showed the values in Table I

The ECG showed inferior fibrosis and ST T abnormalities but the typical perhexiline maleate changes were absent

The clinical picture was interpreted as a severe peripheral neuropathy associated with toxic h patitis probably drug induced Four months after discontinuing the treatment with PM the papilledema was markedly reduced the gait was almost completely normal there was a mild improvement of the lower limb proprioceptive refle s and a mild muscular atrophy was still present

Table I

	Actual velocity	*Normal velocity (range)*
Median nerve	29 2 M /sec	57 71 M /sec.
Ulnar nerve	31 7 M /sec	53 7 73 M./se
Sciatic internal popliteal nerve	29 8 M /sec	40 55 M /sec
Sciatic external popliteal nerve	13 8 M /sec	4? 57 M /sec.

Two months later the EMG showed a dramatic impro ment of the neural conduction speed liver enlargeme however was still present and hepatic enzymes were s elevated (SGOT 56 I U SGPT 28 I U) several months af discontinuing the drug The severe neurological lesions may due to the presence of an undiagnosed liver disease primary secondary to perhexiline maleate leading to a storage of I in the liver and in the neural tissue The former hypothe seems to be more likely since in a group of five patients w normal liver function who had been taking PM in simi large doses conduction abnormalities of the peripheral ner have not been observed

We can conclude that liver function must be assessed befo long term PM therapy is begun while clinical signs of hepa and peripheral nerve involvement should be carefully look for during treatment

Carlo Caruz o M
Gianni Gaschino M.
Cattedra Malattie Apparato Cardiovascola
University of Tu
Walter Troni M
Rossana Cremo M.
Cattedra Neurolog
University of Tu
Turin It

REFERENCES

1 Howard DJ and Russell Rees J Long term perh iline maleate and liver function Br Med J 1 1 1976
2 Abaza A Ciattan D Aziza C L and Pappo I Effects secondaires mais réversibles à la prise de perhe iline Nouv Presse Med 2 28?0 1973
3 Lhermitte F., Fardeau M Chedru F and Mallecou J Poylneuropathy after perhexiline maleate therap Br Med J 1 1256 1976
4 Bourrat Ch Viala J and Guastala J P Neuropath périphérique aprés absorption prolongée de maléate perhexiline Nouv Presse Med 4 25?? 1975

regimen may be inadequate to reduce the hematocrit to a physiological range because arterial oxygen saturation may remain decreased in spite of increasing the inspired oxygen concentration

This study of cerebral blood flow and polycythemia indicates that venesection to a physiological hematocrit may be beneficial for patients with secondary polycythemia because of apparent improvement in central nervous system function mediated by improved cerebral perfusion Venesection should perhaps be repeated until the hematocrit reaches an optimal level of 45% Continuing examination of the effect of rheological alteration on regional flow to all body organs should be pursued

Ernest L York
Richard L Jones
Brian J Sproule
Devidas Menon
Dept of Pulmonary Medicine
and Biomedical Engineering
University of Alberta
Edmonton Alberta T6G 2G3
Canada

REFERENCES

1 Adamson J W The erythropoietin/hematocrit relationship in normal and polycythemic man Implications for marrow regulation Blood 32 597 1968
2 Weil, J V Jamieson G Brown D W Grover R F Bulchrem O J., and Murray J F The red cell mass arterial oxygen relationship in normal man J Clin. Invest 47 1627 1968
3 Vanier L. Dulfano M Wu C and Desforges J F Emphysema hypoxia and the polycythemic response N Engl. J Med 269 169 1963
4 Tura S Pollycove M and Gelpi, S Erthrocyte and iron kinetics in patients with chronic pulmonary emphysema J Nucl Med 3 110 1962
5 Ayvazian L F Richardson D E and Silber R Erythrokinetic studies during antimicrobial therapy in pulmonary emphysema Am Rev Respir Dis 100 305 1969
6 Filley G F Beckwitt H J Reeves J T and Mitchell R S Chronic obstructive bronchopulmonary disease II Oxygen transport in 2 clinical types Am J Med 44 26 1968
7 Dintenfass L Fluidity (internal viscosity) of the erythrocyte and its role in physiology and pathology of circulation Haematologia 2 19 1968
8 Murray J F Karp R B and Nadel J A Viscosity effects on pressure flow relations and vascular resistance in dogs lungs J Appl Physiol 27 336 1969
9 Whittaker S R. F and Winton F R The apparent viscosity of blood flowing in the isolated hind limb of the dog and its variation with corpuscular concentration J Physiol London 78 339 1933
10 Segel N., and Bishop J M. The circulation in patients with chronic bronchitis and emphysema at rest and during exercise with special reference to the influence of changes in blood viscosity and blood volume on the pulmonary circulation J Clin Invest. 45 1555 1966
11 Auchincloss J H Jr., and Duggan J J Effects of venesection on pulmonary and cardiac function in patients with chronic pulmonary emphysema and secondary polycythemia Am J Med. 22 74 1957
12 Dayton L M Morgantown W Va McCollough R E., Weil J V Scheinhorn D F., and Filley G F The effects of phlebotomy on lung function in secondary polycythemia Am Rev Respir Dis 107 1112 1973
13 Massaro D and Katz S Effect of venesection on arterial gas values and ventilatory function in patients with chronic bronchitis, Thorax 20 441 1965
14 Rakita L. Gillespie D G and Sancetta S M The acute and chronic effects of phlebotomy on general hemodynamics and pulmonary functions of patients with secondary polycythemia associated with pulmonary emphysema AM HEART J 70 466 1965
15 Harrison B D W Davis J Madgwick R G and Evans M The effects of therapeutic decrease in packed cell volume on the responses to exercise of patients with polycythemia secondary to lung disease Clin Sci. Mol Med 45 833 1973
16 York, E L Jones R L Menon D., and Sproule B J Effects of secondary polycythemia on cerebral blood flow in chronic obstructive pulmonary disease Am Rev Respir Dis. 121 813 1980
17 Thomas D J du Boulay G H., Marshall, J., Pearson T C., Ross Russell R W Symon L. Wetherley Mein G and Zilkha E Cerebral blood flow in polycythaemia Lancet 2 161 1977
18 Weir B K. A. Menon D and Overton T R Regional cerebral blood flow in patients with aneurysms. Estimation by 133 Xenon inhalation Can J Neur Sci. 5 301 1978
19 Thomas, D J du Boulay G H Marshall, J., Pearson T C., Ross Russell R W Symon L., Wetherley Mein G and Jilkha E Effect of haematocrit on cerebral blood flow in man Lancet 2 941 1977
20 Neff L A., and Petty T L. Long term continuous oxygen therapy in chronic airway obstruction. Mortality in relationship to cor pulmonale hypoxia and hypercapnia Ann Intern Med 72 621 1970
21 Petty T L and Finigan M W Clinical evaluation of prolonged ambulatory oxygen therapy in chronic airway obstruction Am J Med 45 242 1968
22 Chamberlain D A and Millard F J C The treatment of polycythaemia secondary to hypoxic lung disease by continuous oxygen administration Q J Med. 32 341 1963

entazocine No patient had received antiarrhythmic drugs Ve do not think that data from this latter group had a oticeable value in the context of our report and for this ason we had omitted relating them

We are aware that verapamil can reveal a latent sick sinus ndrome or induce hypotension because of this (as previous stated in our Letter) we avoided using the drug in patients ith sinus bradycardia or systolic blood pressure lower than 00 mm Hg Although these seem to be logical precautions we ave never observed undesirable side effects

With regard to the possibility that the disappearance of entricular premature beats (VPBs) had taken place sponta eously instead of being a drug effect we think that unlikely nce rapid disappearance of VPBs occurred in 85% of the atients also the lack of relapses for at least three hours after rug injection can hardly be considered fortuitous When PBs are treated with a bolus of lidocaine in most cases it is ecessary to prolong the infusion of the drug thus suggesting hat VPBs of acute myocardial infarction are not always ransitory Moreover many reports prove that the effect of erapamil given as a bolus intravenously is not attenuated ompletely in 10 minutes but show that the pharmacological ffects of the drug last longer—thus suggesting a longer alf life and/or a preferential myocardial uptake and binding f verapamil

Finally we would like to make some comments about Dr hmad s statement that verapamil has no value in the control f ventricular arrhythmias We too for a long time were onvinced of this and have considered (and still do) verapamil he drug of choice in the treatment and prophylaxis of paroxysmal supraventricular tachycardia However the ncreasing experimental evidence that arrhythmias following acute myocardial infarction can be related to the slow response action potentials led us to verify the usefulness of a drug (such as verapamil) which inhibits slow responses in treatment of VPBs of acute myocardial infarction Our results are positive and support the hypothesis that in man VBPs of acute ischemia are also related to the slow inward current.

The distinction of ventricular arrhythmias on the basis of the activating current seems to us to be a very important advancement in arrhythmology

P F Fazzini MD
F Marchi MD
P Pucci MD
Division of Cardiolog
Santa Maria Nuova Hospital Florence
F Ledda MD
A Mugelli MD
Department of Pharmacolog
Section of Cardiac Electrophysiolog
University of Florenc
Florence Ital

REFERENCES

1. Fazzini P F Marchi F Pucci, P Ledda F an Mugelli A Effects of verapamil on ventricular prema ture beats of acute myocardial infarction AM HEART J **98** 816 1979
2. Schomerus M Spiegelhalder B Stieren B and Eichel baum M Physiological disposition of verapamil in ma Cardiovasc Res **10** 605 1976
3. Neugebauer G Comparative cardiovascular actions of verapamil and its major metabolites in the anaesthetise dog Cardiovasc Res **12** 247 1978
4. McAllister R G Jr Bourne D W A and Ditter L W The pharmacology of verapamil. Eliminatio kinetics in dogs and correlation of plasma levels wit effect on the electrocardiogram J Pharmacol. Ex Ther **202** 38 1977

Reply

To the Editor:

In our series there were no serious side effects, mainly because it was a short term study and none of the patients took perhexiline maleate for more than six weeks. Serious neurological complications have been observed among those who have taken perhexiline on a long term basis, as happened in the case reported here by Dr Carruzzo and colleagues. These workers suggest that neuropathy may be due to liver disease in patients taking perhexiline. In our series serum transaminases were raised in about 30% of patients and other workers have reported abnormal liver function tests in 10% to 17% of patients, whereas the incidence of neuropathy is about 0.1% in patients taking perhexiline. Subclinical neuropathy indicated by abnormal electrophysiological measurements, occurs in two thirds of patients—a substantially higher proportion of patients than those who develop clinically recognizable neuropathy. It is obvious that abnormal electrophysiological tests and abnormal liver function tests do not help in finding the patients at risk for developing the neurological syndrome. The only way one can guard against such serious complications is by seeing the patients every month or six weeks, by examining them for serious loss of weight, questioning closely for early symptoms of neuropathy (i.e., numbness, tingling etc.) and by repeating liver function tests. Most workers would agree that the drug should be stopped if a patient continues to lose weight, develops early signs of neuropathy, or if liver function tests deteriorate or remain persistently abnormal.

An early withdrawal of perhexiline is important since most of the complications caused by this drug are reversible.

M. A. Mir, M.B., M.R.C.P., D.C.H.
Department of Medicine
Welsh National School of Medicine and
University Hospital of Wales
Heath Park, Cardiff
CF4 4XN, Wales
United Kingdom

REFERENCES

1. Newborne J W: Assessment of safety data from patients on short and long term perhexiline therapy. Postgrad Med J 49(Suppl):125, 1973.
2. Morledge J: Effects of perhexiline maleate in angina pectoris: a double blind clinical evaluation with ECG treadmill exercise testing. Postgrad Med J 49(Suppl):64, 1973.
3. Argov Z, and Mastaglia F L: Drug induced peripheral neuropathies. Br Med J 1:663, 1979.
4. Sebille, A: Prevalence of latent peripheral neuropathy. Br Med J 1:1321, 1978.

Verapamil therapy

To the Editor:

A recent Letter to the Editor by Fazzini and associates warrants further comments. They state that 28 patients with myocardial infarction who presented with frequent ventricular premature beats (VPBs) in the first 48 hours of their illness were treated with intravenous verapamil. They failed to mention these patients' ages, any concomitant therapy, or any other associated disease.

Rosing and colleagues have recently reported a 77-year-old woman who developed sinus arrest and hypotension following one 80 mg oral verapamil capsule. It is noteworthy to stress that this patient had manifested no findings that would have been suggestive of sick sinus syndrome.

Verapamil, given as a bolus intravenously, has a very short half life and its effect is attenuated completely within 10 minutes. It is therefore not clear whether the disappearance of VPBs up to three hours after verapamil was due to the effect of this drug or occurred spontaneously.

Systemic hypotension and prolongation of PR interval are the commonest side effects of verapamil[3]. I strongly believe that this drug has no place in the management of VPBs of acute myocardial infarction. Furthermore, verapamil appears to be of no value in the control of ventricular arrhythmia. Verapamil depresses the sinus discharge rate; therefore it is contraindicated in patients with sinoatrial disease, which usually may be found in the older population. Of course verapamil is the drug of choice in the treatment and prophylaxis of paroxysmal supraventricular tachycardia.[4]

Finally, I should emphasize that verapamil should not be used within 48 hours after administering beta adrenergic blockers, disopyramide or quinidine therapy. Physicians caring for patients with cardiac arrhythmia should bear in mind the possible drug interactions and side effects of verapamil and be more selective in choosing patients for treatment with this agent. Nevertheless, the introduction of verapamil will constitute a very significant advance in cardiovascular therapeutics in this country.

Saeed Ahmad, M.D., M.R.C.P., F.C.C.P.
Senior Attending Physician and Vice Chairman
Department of Medicine
Fairmont General Hospital
Fairmont, W. Va. 26554

REFERENCES

1. Fazzini, P F, Marchi, F., Pucci, P., Ledda, F., and Mugelli A: Effects of verapamil on ventricular premature beats of acute myocardial infarction. AM HEART J 98:816, 1979.
2. Rosing D R, Kent K M, Maron, B J., and Epstein S E: Verapamil therapy: A new approach to the pharmacologic treatment of hypertrophic cardiomyopathy. Circulation 60:1208, 1979.
3. Aronow W S, Landa D., Plasencia, G., Wong R., Karlesberg, R. P., and Ferlinz, J: Verapamil in atrial fibrillation and atrial flutter. Clin. Pharmacol. Ther 26:578, 1979.
4. Singh, B N: Drug lag in therapy of arrhythmia and angina, Primary Cardiol. 5:45, 1979.

Reply

To the Editor:

We wish to thank Dr. Ahmad for his observations.

The age of our patients ranged between 40 and 65 years; the mean age was 58 years. Systemic hypertension was present in nine patients and diabetes mellitus was present in four. Fifteen patients had received nitrates and 20 had received

Announcements

Eighth Annual Cardiac Symposium

The Department of Medicine and Cardiac Rehabilitation of Georgia Baptist Medical Center will present its Eighth Annual Cardiac Symposium in Atlanta on October 10 1980 The guest lecturer will be William Kannel, M D Co-directors of the symposium are Gerald F Fletcher M D., and John D Cantwell, M.D For further information contact Gerald F Fletcher M.D., Director of Internal Medicine, 300 Boulevard N E., Atlanta, Ga. 30312

Joint Conference on Stroke and Cerebral Circulation

The Stroke Council of the American Heart Association, in association with the Cerebrovascular Surgery Section of the American Association of Neurological Surgeons, The Canadian Stroke Society of the Canadian Heart Foundation and The Society for Vascular Surgery will present a Sixth International Joint Conference on Stroke and Cerebral Circulation at the Century Plaza Hotel in Los Angeles on February 12 through 14 1981 The conference is an open meeting, whose purpose is to provide a common forum for the presentation of material relating to all aspects of cerebrovascular disease and the physiology and pathology of the cerebral circulation Abstracts dealing with the clinical or experimental aspects of the pathogenesis, diagnosis, medical and surgical management of vascular disease of the brain and spinal cord are welcome Deadline for the receipt of abstracts is August 29 1980 (postmarked) Accepted abstracts will be published in the January 1981 issue of the journal *Stroke* of the American Heart Association.

Guidelines and further information may be obtained from Administrator Postgraduate Programs, American Heart Association, 7320 Greenville Ave., Dallas, Texas 75231 Telephone (214) 750-5441

Cardiac Imaging and Cardiovascular Radiology

A course entitled "Cardiac imaging and review of cardiovascular radiology for residents and fellows," will be presented April 1 through 4 1981 at the Islandia Hyatt House in San Diego California, by the Faculty of the Department of Radiology of the University of California, San Diego Medical Center Program Director is Michael J Kelley M D For further information, contact Mary J Ryal Radiology P O Box 2305 La Jolla, Calif 920?? Telephone (714) 459 9787

Lucien Dautrebande Pathophysiology Prize for 1979

The Professeur Lucien Dautrebande prize for 1979 in the amount of $37 000 has been awarded to Professor J E Desmedt Director of the Brain Research Unit Faculty of Medicine of the University of Brussels, Brussels, Belgium. Dr Desmedt has been chosen by an international jury for his original contributions to neuromuscular diseases, to the mechanisms of voluntary motor control in man, and to brain mechanisms studied by the evoked potentials method in relation to maturation aging neurological disorders, and cognitive performance After receiving the Dautrebande prize from the hands of H.M Queen Fabiola of the Belgians, Dr Desmedt emphasized in his acceptance speech the increasing importance of the systems approach of pathophysiology and of the development of physiological methods applied to intact man.

The next competition for the Dautreband Prize will be held in 1982 and the award will be approximately $46 000 All particulars may be secured by writing to Dr Stalport, President 35 chausee de Liége 5200 Huy Belgium. For consideration in the 1982 competition, all papers must be received *before* December 15 1981.

Society of Nuclear Medicine Meeting

The Eighteenth Annual Meeting of the Society of Nuclear Medicine will be held in September 1980 in Erlangen/Nurnberg W Germany The main theme of the meeting is "Nuclear Medicine with its Interdependencies," with special reference to cardiology and hepatogastroenterology For further information, contact Prof Dr F Wolf, 18th International Annual Meeting Society of Nuclear Medicine, Institut und Poliklinik fur Nuklearmedizin der Universitat Erlangen Nurnberg Krankenhausstrasse 12 D-8500 Erlangen W Germany Telephone 09131/853411 153416

Book reviews

Ambulatory ECG Monitoring Edited by Shlomo Stern M D F.A.C.C., London and Chicago 1978 Year Book Medical Publishers, 197 pages.

This small book edited by Stern and with several contributors reviews the technic and problems associated with applications of ambulatory monitoring The book is clinically oriented The 14 chapters review very well many problems related to Holter monitoring The use of the monitor in the evaluation of arrhythmias effects of therapeutic agents and the results of cardiac management are clearly discussed The book describes thoroughly and very well the application of Holter monitoring The illustrations are good and the book should be available to all cardiologists and other physicians who use ambulatory monitoring This is a good book but it does not represent a critical discussion of the limitations applications, and abuses concerned with Holter monitoring

Progress in Cardiology Vol 7 Edited by Paul N Yu M D and John F Goodwin M.D., Philadelphia 1978 Lea & Febiger 228 Pages. Price $17 00

This is the seventh volume of the *Progress of Cardiology* The subjects discussed vary widely in the field of cardiology They include discussions of embryology the role of the nervous systems in cardiovascular control emotions catecholamines and the electrocardiogram diet drugs and pulmonary hypertension and angina pectoris new operations for congenital cardiac anomalies and recent advances in peripheral vascular disease The eight chapters are written for the clinician and housestaff in training in internal medicine and cardiology This is another good volume and the subjects discussed are not only interesting but important

Dynamic Cardiac Auscultation and Phonocardiography By Abner J Delmar M.D F.A.C.P., F.A.C.C and Emanuel Stein M.D., M.P.H., F.A.C.P., F.A.C.C F.C.C.P Philadelphia 1979 W B Saunders Company 1023 pages. Price $55 00

This is an atlas of over one thousand pages of excellent illustrations of simultaneous recordings of heart sounds apex cardiograms phases of respiration and a reference ECG Carotid pulse tracings are included in most of the illustrations The associated text is clearly written and the legends are quite helpful Readers will find this to be an excellent review of phonocardiography Page 181 contains an interesting illustration of mid systolic click" which does not occur in mid systole but rather in late systole This illustration for example clearly indicates the looseness of nomenclature and definition of findings The Whoop or Honk is nicely illustrated on page 183 The book is very good The illustrations are excellent This book should be of value to all cardiologists internists and trainees in internal medicine and cardiology Careful and thoughtful study of this book should improve every clinician s cardiac auscultation

Advances in Cardiology: New Approaches in the Diagnosis and Management of Cardiovascular Disease Edited by John H K Vogel Basel, 1979 S Karger AG., 139 pages Price $53.50

This issue of *Advances in Cardiology* is concerned with both diagnosis and treatment The many contributors review effectively noninvasive techniques use of positron-emitting radionuclides use of propranolol and newer antihypertensive drugs pharmacologic treatment of patent ductus arteriosus diet exercise medical and surgical management of unstable angina surgical treatment of congenital heart disease and other important cardiovascular problems. The respective short reviews were presented at the Ninth Cardiovascular Conference held at Snowmass The presentations are interesting and should prove of considerable value to cardiologists as well as to non-cardiologists The subjects discussed are timely such as the results of medical and surgical management of unstable angina

Coronary Artery Disease Recognition and Management. By Charles E Rackley M D and Richard O Russell Jr M D., New York 1979 Futura Publishing Company 439 pages Price $33 00

This book edited by Rackley and Russell with 14 additional contributors, reviews very well the contemporary approach to the diagnosis and management of coronary artery disease The 15 chapters include discussions of the natural history of coronary artery disease precordial movement echocardiography radionuclide studies exercise testing clinical syndromes of coronary artery disease coronary arteriography cardiac catheterization use of nitrates myocardial metabolism bypass surgery diagnosis and management of acute myocardial infarction. The illustrations are good and a useful bibliography is provided This is a good review of many important aspects of the diagnosis and management of coronary artery disease It is rather interesting that the role of electrocardiography is neglected in the considerations, whereas the newer more complex procedures are given prominent exposure This book should be of interest to readers who are interested in learning the role of these newer procedures in cardiology Readers will find this a useful book especially housestaff and trainees in cardiology

Books received

Functional Evaluation and Rehabilitation of Cardiac Patients Edited by Paolo Rossi, M D Chicago 1979 Year Book Medical Publishers, Inc 384 pages Price $37 50

Cardiovascular Physiology for Anesthesiologists By Ronald J Gordon Ph.D Mark B Ravin M D and George R Daicoff M D Springfield Ill. 1979 Charles C Thomas Publisher 709 pages Price $19 75

Shock Trauma Manual By William Gill M.D., and William B Long M D., Baltimore 1979 The Williams & Wilkins Company 283 pages. Price $18 00

Pediatric Cardiology By Courtney L. Anthony M D., Rica G Arnon M D., and Charles W Fitch, M D Garden City N Y., 1979 Medical Examination Publishing Co., 534 pages. Price $16.50

etc) cardiovascular symptoms (exertional chest pain dyspnea and leg pain) socio personal characteristics (educational level consumption of alcohol coffee etc), metabolic and miscellaneous features (cholesterol uric acid leukocyte count forced vital capacity etc)

The results obtained were essentially consistent for all race sex groups Smokers who later quit (ex smokers) showed statistically significant differences from smokers who continued the habit in a number of cardiovascular symptoms socio personal characteristics and metabolic and miscellaneous traits In the 288 comparisons made with persistent smokers the ex smokers at index examination were statistically different in 130 or 45% at the $p < 05$ level, and the majority of these (84) were significant at the $p < 01$ level Controlling for smoking quantity had little effect on the observed differences between the persistent quitters and persistent smokers Furthermore at index examination (when still smoking) the ex smokers characteristics were not very dissimilar from those of nonsmokers Thus the investigation clearly indicated that ex smokers are not a representative sample of smokers with regard to their CHD related characteristics or the extent of the smoking habit And, most importantly the nature of the differences revealed that smokers destined to quit (ex smokers) showed characteristics at baseline indicative of *lower CHD risk* than smokers destined to continue

The findings of our study prompt the following conclusions The observational studies referred to above which show lower CHD rates for ex smokers than for continuing smokers are flawed having failed to observe the basic principles of valid scientific inference Their comparisons of the CHD outcomes of the two groups are *biased* since they have made the false assumption that ex smokers are representative of continuing smokers except for the change in the smoking habit With ex smokers self selected to begin with and at lower CHD risk at baseline it is small wonder that their CHD outcomes in these widely publicized studies are found to be lower than those of continuing smokers The extent to which the CHD outcomes are lower than those of continuing smokers resulting from baseline differences remains to be determined

The results of our new study have received strong support from Rose and Hamilton in their recently published report on a randomized controlled trial of smoking cessation in middle aged English male civil servants at high risk of cardiorespiratory disease After almost eight years of follow up they found no significant differences in mortality rate between the intervention group and the normal care group despite the greater cigarette smoking cessation (58% at 3 years) in the intervention series than in the normal care group (14% at 3 years) The authors state the interpretation of these observational studies [3] is not straightforward for men who stop smoking are not a representative sample of smokers comparison of the two groups is biased the reversibility of the risk of cigarettes to the smoker s life may have been overestimated in observational studies Disappointingly we find no evidence at all of any reduction in total mortality

What are we then to believe about the effect of stopping smoking on the risk of CHD? Despite the conventional view that cessation of smoking reduces the risk of mortality from heart disease there is now evidence that the comparisons of the CHD outcomes between ex smokers and smokers in the observational studies are biased and *unreliable* Our new study reported above indicates that ex smokers at baseline are at lower CHD risk to begin with thus contributing to their eventual lower CHD outcomes In addition the results of the first randomized controlled trial of the possible effect of smoking cessation in middle-aged men have shown no improvement in their rate of mortality relative to those who were not urged to stop smoking thus the reversibility of the claimed risk of cigarettes to the smoker s life has not been demonstrated Accordingly it is reasonable to believe there is no proof that stopping reduces the risk of heart disease

Surgeon General s Report—1979

The second event bearing on the question of smoking and CHD is the publication of the Surgeon General s 1979 Report on Smoking and Health The 1979 Report summarizes its views on smoking and cardiovascular diseases as follows In summary for the purposes of preventive medicine it can be concluded that smoking is causally related to coronary heart disease for both men and women in the United States Unfortunately the text of the report fails to validate the conclusion

The main thrust of the 1979 Report is with the

American Heart Journal

September 1980 Volume 100 Number 3

Editorial

Smoking and coronary heart disease what are we to believe?

Carl C Seltzer Ph D
Cambridge Mass

Two recent events have raised serious questions as to what we are to believe about the conventional view that cigarette smoking is a cause of coronary heart disease (CHD)

Interpretation of ex smoker data

The first event relates to the interpretation of ex smoker data indicating that CHD mortality rates of persons who stopped smoking are substantially lower than those of persons who continued smoking The interpretation given to these data is that smoking cessation directly results in the reduction of risk of heart disease mortality The most commonly cited investigations in support of this line of thinking are the observational studies of Doll and Hill s British doctors Hammond s American men and women Kahn s U S veterans and the Framingham Study Underlying this alleged CHD benefit however is the assumption that ex smokers are a representative sample of smokers except in so far as they have stopped smoking But the proof of the validity of this assumption has not been forthcoming This is a crucial point in the comparison of the CHD outcomes in the two smoking groups For if the assumption of representativeness is invalid and significant baseline differences are observed between ex smokers and smokers for relevant factors then the possibility exists that the mortality comparison of ex smokers and continuing smokers is biased

For the first time in a very large series of subjects according to race and sex we observed the proper baseline for the determination of whether or not ex smokers were a representative sample of smokers This baseline involved the study of the CHD related characteristics of ex smokers *before they stopped smoking* and their comparison with those of persistent smokers The results of this study are briefly reviewed below

Using the longitudinal records from the Kaiser Permanente multiphasic health check ups the study compared 25 CHD related characteristics of ex smokers *before they stopped smoking* with those of persistent smokers and nonsmokers A total of more than 25 000 subjects white men and women black men and women with three or more consecutive health check ups formed the basis of the analysis For the criteria of the classification of the subjects the designated index examination and the list of CHD related characteristics the reader is referred to the publication [5] The minimum of three or more examinations was used in order to insure a rigorous classification of the smoking categories Thus ex smokers (persistent quitters) were subjects who had at least one examination at which they reported both a current and past history of cigarette smoking followed by at least two examinations in which they reported complete cessation of smoking The CHD related characteristics fell into arbitrary categories cardiovascular manifestations (blood pressure hypertension

Received for publication July 19 19 9

Reprint requests Carl C Seltzer Ph D Harvard University 11 Divinity Ave Cambridge Mass 0 13

Honorary Senior Research Associate Harvard University

0002-8 03/80/090?75 + 06$00 60 0 © 1980 The C V Mosby Co

Thus after many years of search and experimentation the mechanisms by which smoking (cigarette smoke) might enhance various manifestations of CHD have not been satisfactorily established Many hypotheses have been advanced as explanations of possible pathways between smoking and enhancement of CHD but these remain postulations To arrive at a conclusion that smoking is causally related to CHD proven mechanisms are the essential links between the evidence of statistical association of smokers with excess CHD in a number of countries These proven mechanisms have not been forthcoming

There are a number of other aspects of smoking and CHD in the 1979 Report which are not supportive of the causal hypothesis For example angina pectoris an important manifestation of CHD is not deemed to be at risk from smoking In this connection the 1979 Report states the predictive risk factor association of smoking with the incidence of angina pectoris is not clear and epidemiological data on the association between cigarette smoking and angina pectoris and cerebrovascular disease manifested as stroke are not conclusive

In discussing the effect of smoking on blood lipids the 1979 Report finds that The data are not very uniform As for cholesterol its association with smoking is minimized stating that There may indeed be a minor tendency for cigarette smokers to have slightly elevated blood cholesterol levels for whatever reasons And in discussing cholesterol levels in the Framingham Study it is concluded that These differences were too small to account for the observed difference in risk associated with type of smoking habit Also with regard to the Tromso and Framingham studies the 1979 Report asserts that almost identi[illegible]al HDL cholesterol levels among smokers and non[illegible]mokers were found there was no significant [illegible]sociation between them

The 1979 Report al[illegible]l[illegible]es the effect of smoking on the [illegible] tem in proper context It [illegible]ates The [illegible]nd transient effect of smoking [illegible] man is [illegible] heart rate and blood pressure t[illegible] The relationship between [illegible]rt[illegible]ion is made crystal clear in [illegible]tations Available data indicat[illegible] not a major risk factor for hypertension and in practice the association is slightly negative — Cigarette smoking does not induce chronic hypertension — There is no apparent relationship between smoking and incidence of hypertension

The 1979 Report is also notable for what it does not mention or fails to give adequate attention to No mention is made that there is an absence of excess CHD risk in the elderly (ages 65 and over) in the continuation of cigarette smoking[1] No mention is made that the evidence of an association between CHD and duration of cigarette smoking is not clear owing to the absence of such an association in the Framingham Study th[illegible] Albany Heart Study Dorn s U S veterans study and the Canadian veterans study[11] No mention is made of the importance of other variables known to be important in CHD (in their confounding effects) such as educational level income class marital status occupation job advancement and ethnicity[1] The 1979 Report concludes that cigarette smoking is causally related in United States women but fails to mention that the Framingham Study (the U S Public Health Service s own study) found essentially no relation between cigarette smoking and heart disease in women[18] The constitutional hypothesis is dogmatically dismissed principally on the basis that "risk of smokers reverts to normal or nonsmokers level after they cease to smoke necessitating a change in ex smokers in their constitutional factor in midlife Such a view shows a disturbing lack of understanding of the constitutional hypothesis and is contrary to the evidence that ex smoker CHD rates are related to their basic characteristics rather than to a flat out ascription to smoking cessation The evidence of a constitutional genetic factor from the data of twin studies is stated to be inconclusive despite the consistent results of Cederlof and colleagues[7], Friberg and associates[1] Lundman[9] Liljefors and De Faire[1] No mention is made of Burch s contention that the secular trends in sex specific and age specific death rates from CHD in England and Wales (1921 1973) strongly support the constitutional hypothesis[23]

Apart from the matter of association perhaps the most common argument raised in behalf of the causal hypothesis is that stopping smoking reduces the risk of CHD This has been considered by the American Heart Association s 1977 Ad Hoc

statistical association of cigarette smoking and CHD The association showing smokers relative to nonsmokers having more specific manifestations of CHD in the form of myocardial infarction and sudden death is evident So is the association of smokers with necropsy manifestations of atherosclerosis These conditions have strong appeal to epidemiologists and others to draw causal conclusions as to the effect of smoking on CHD despite the universal dictum stated by the 1979 Report that ' correlation is not synonymous with causation Beyond the matter of statistical association of smokers with myocardial infarction sudden death and atherosclerosis (from necropsy) the *necessary evidence of a causal connection is not* clear nor determined The cold reality is that the mechanisms by which smoking (tobacco smoke) allegedly enhances CHD have not been established As far back as 1964 the Surgeon General s Advisory Committee on Smoking and Health found no unique cardiovascular effects were demonstrated to seem likely to account for the observed associations of cigarette smoking [smokers] with an increased incidence of coronary disease Since then however many hypothetical mechanisms have been advanced starting with the Surgeon General s 1967 Report[1] successively to the latest 1979 Report Facile postulations have been the order of the day with nicotine and carbon monoxide featuring among the guilty culprits

At times the 1979 Report is quite candid as to what is known concerning the mechanisms by which cigarette smoke affects various aspects of CHD With regard to atherogenesis the 1979 Report states At the present time animal experiments on atherogenesis and CO have provided conflicting data and must be regarded as unsatisfactory Further The *mechanisms* by which smoking enhances atherogenesis require elucidation And still further specific morphological features of plaques that would be characteristic of smoking have not been delineated And again The *overall impression from available data is* that nicotine does not affect atherogenesis in animals The summary on this subject seems very weak First it remarks there is no reasonable doubt that cigarette smoking enhances *atherogenesis* while *further on in the* same summary section it confesses that Relatively little is known about the mechanisms by which smoking enhances atherogenesis or increases the risk of heart attack The 1979 Report is singularly maladroit in summarizing this area of concern

In connection with myocardial infarction the 1979 Report states The mechanism of effect is usually attributed to an enhancement of coronary atherosclerosis in smokers and the consequent occurrence of cardiac ischemia and ischemic necrosis of heart muscle Myocardial infarction then is attributed to the smoking enhancement of atherosclerosis which at present is based on speculation or doctrinal statements rather than on rigorously interpreted evidence Note the following quotations it can be *hypothesized* (my *italics*) *that patients on the* border of myocardial ischemia may be pushed into impending or actual infarction by the effects of nicotine and CO and it may be *speculated* (my italics) that in the presence of coronary atherosclerosis of a degree insufficient to cause ischemia the action of smoking on platelet pathophysiology may precipitate occlusive thrombosis and infarction No wonder the 1979 Report finds A major need is to understand better the mechanisms by which smoking can induce or affect the evolution of myocardial infarction

As for the mechanisms by which smoking may precipitate sudden cardiac death the 1979 Report states The mechanisms *postulated* (my italics) to explain the association of sudden cardiac death with smoking have been described under atherogenesis and under myocardial infarction as *possible* (my italics) mechanisms for effects of smoke nicotine and CO It is of collateral interest that the 1979 Report finds that The act of cigarette smoking does not appear to be immediately related in time to sudden death The section on sudden death is concluded with the following The mechanisms by which smoking might induce sudden death in addition to an exacerbation of coronary artery arteriosclerosis can be *hypothesized* (my italics) from experiments that indicate that an exacerbation of regional ischemia *may promote electrical instability of the heart* fibrillation or asystole Further research will be required if these mechanisms are to be well understood and if they are to be shown to be actual mechanisms in man in relation to smoking *and sudden death* Medicine will agree with the 1979 Report when it states The mechanisms of sudden death its precursor states and preventive therapy require further elucidation

Health Service Publication No 1103 Washington DC 1964
10 The health consequences of smoking a Public Health Service review 1967 U S Dept of Health Education and Welfare Public Health Service Publication No 1696 Washington DC 1967
11 Seltzer C C Smoking and coronary heart disease in the elderly Am J Med Sci 269 309 1975
12 Editorial Smoking in the elderly Br Med J 4 607 1975
13 Seltzer C C The absence of excess coronary heart disease among the elderly in the continuation of cigarette smoking a reply Am J Med Sci 276 18 1978
14 Seltzer C C Smoking and cardiovascular disease Am Heart J 90 125 197
15 Buechley R W., Key C R Morris D L Morton W F and Morgan M V Altitude and ischemic heart disease in tricultural New Mexico An example of confounding Am J Epidemiol 109 663 1979
16 Dawber T R Risk factors for atherosclerotic disease Current concepts The Upjohn Company 1975
17 Cederlof R. Friberg L., and Jonsson E Hereditary factors and "angina pectoris" A study on 5 877 twin pairs with the aid of mailed questionnaires Arch Environ Health 14 397 1967
18 Friberg L Cederlof R and Lundman T The interaction of smoking environment and heredity and the implications for disease etiology A report on the Swedish twin registries Acta Med Scand. Suppl 612 197
19 Lundman T Smoking in relation to coronary heart disease and lung function in twins A co twin control study Acta Med Scand Suppl. 115 1966
20 Liljefors I Coronary heart disease in male twins Seven year follow up of discordant pairs Acta Genet Med Gemellol 25 2 1976
21 De Faire U Ischemic heart disease in death-discordant twins A study on 205 male and female pairs with special reference to hereditary factors Acta Med Gemellol 25-271 1976
22 Burch, P R J Coronary disease Risk factors age and time Am Heart J 97 415 1979
23 Kannel, W B Doyle J T Frederickson D T and Harlan W R Revised ad hoc committee report on cigarette smoking and cardiovascular diseases American Heart Association 197

Information for authors

Most of the pr visions of the Copyright Act of 1976 became effective on January 1 1978 Therefore all ma cripts mu t be accompanied by the following written statement signed by one auth r [illegible] undersigned author transfers all copyright ownership of the manuscript [illegible] article) to The C V Mosby Company in the event the work is published [illegible] igned author warrants that the article is original is not under con [illegible] her journal and has not been previously published I sign for and accep [illegible] tor releasing this material on behalf of any and all co authors Author [illegible] ted when po sible regarding republication of their material

Committee on Cigarette Smoking and Cardiovascular Diseases as the final link in the chain of evidence incriminating cigarette smoking as a causal factor in cardiovascular disease The 1979 Report asserts that Cessation of cigarette smoking reduces over time the increased risk attributable to smoking toward the risk of nonsmokers That these views are untenable is now apparent from the new evidence we presented in the first part of this article

Conclusions

What then remains in the 1979 Report on CHD with which we can readily agree? We can agree with the 1979 Report that coronary atherosclerosis is of primary importance in the development of CHD through myocardial ischemia We can agree that the available necropsy data indicate that cigarette smokers tend to have more severe and extensive atherosclerosis of the coronary arteries than nonsmokers But this does not mean *ipso facto* that cigarette smoking enhances atherosclerosis for the mechanism(s) by which smoking might enhance atherogenesis or increase the risk of heart attack have not been established There have been no consistent clinical or experimental data in animals or man that clearly support the leap from association to enhancement

We can also agree that there is a statistical association between cigarette smoking and CHD in the United States While it is true as well with regard to some western European countries no significant statistical associations between smoking and CHD have been reported in Finland the Netherlands Italy Greece Yugoslavia Japan and Puerto Rico[14] No convincing evidence has been forthcoming to account for the absence of associations in so many countries some of which are not too far removed in their nutritional and metabolic circumstances from the U S This explains the stricture in the summary statement in the 1979 Report limiting the conclusion to men and women in the United States

Accordingly the statistical associations of cigarette smokers with atherogenesis myocardial infarction and sudden death in a limited geographical sense are what remains from the assertion that smoking is causally related to CHD Since as the 1979 Report points out mere association is not synonymous with causation this is insufficient for valid scientific inference without attendant support from clinical and experimental data This attendant support is lacking since the necessary mechanisms indicating how cigarette smoking might possibly enhance CHD are either unknown or not established and owing to the absence of proof that stopping smoking reduces CHD

The associations however still remain to be explained In the case of ex smokers we found that self selection appeared to be responsible for the differences in CHD outcomes between ex smokers and continuing smokers That self selection may also be the basis of the CHD differences between smokers and nonsmokers has not been ruled out The crucial study of baseline characteristics of smokers and nonsmokers remains to be performed by epidemiologists The constitutional hypothesis must be examined closely and without prejudice for possible explanations

For the present then it is reasonable to believe that stopping smoking does not reduce the risk of CHD and that there is no established proof that cigarette smoking is causally related to coronary heart disease

REFERENCES

1 Doll R and Hill A B Mortality in relation to smoking ten years observations of British doctors Br Med J 1 1339 1964
2 Hammond E C Smoking in relation to the death rate of one million men and women Natl Cancer Inst Monogr No 19 pp 127 204 Bethesda Maryland 1966
3 Kahn H A The Dorn study of smoking and mortality among U S veterans report of eight and one-half years of observation Natl Cancer Inst Monogr 19 1 1966
4 Gordon T Kannel, W B and McGee D Death and coronary attacks in men after giving up cigarette smoking A report from the Framingham Study Lancet ii 1345 19 4
5 Friedman G D Siegelaub A B Dales, L G and Seltzer C C Characteristics predictive of coronary heart disease in ex smokers before they stopped smoking Comparison with persistent smokers and nonsmokers J Chronic Dis 32 1̄5 1979
6 Rose G and Hamilton P J S A randomised controlled trial of the effect on middle-aged men of advice to stop smoking J Epidemiol Community Health 32 ? 5 1978
7 The health consequences of smoking U S Dept of Health Education and Welfare HEW publication No 78-8357 Washington D C 19̄6
8 Smokin and Health a report of the Surgeon General, U S Dept of Health Education and Welfare HEW publication no 9 50066 Washington D C 19/9
9 Smoking and Health report of the advisory committee to the Surgeon General of the Public Health Service U S Dept of Health Education and Welfare Public

Table 1 Clinical and electrocardiographic data

Case	Sex	Sport	*First observation* Age (yrs)	*First observation* Resting ECG features	*Last observation* Age (yrs)	*Last observation* Resting ECG features	Remarks
1	M	Marathon	22	Wenckebach	–	–	Normalization of A V conduc after sympathetic maneuve drugs exercise AVD after pine
2	M	Skating	15	Normal A V conduction	20	Wenckebach	Valsalva phase 4 induced Wenckebach Normalization of A V conduction after sympathetic maneuvers drugs exercise E after atropine
3	M	Walking	24	Wenckebach	–	–	Normalization of A V condu after sympathetic maneuv drugs exercise
4	M	Skiing	20	Wenckebach	–	–	Probable dual A V nodal pathway Normalization of A V conduction after drugs and exercise Poor sinus node response to atropine
5	M	Swimming	13¼	Wenckebach	15	1 (PR 0 24 to 0 36)	Normalization of A V conduction after sympathetic maneuvers, drugs exercise
6	M	Basketball	19	Wenckebach	20¼	Wenckebach EAR	Normalization of A V conduction after sympathetic maneuvers and exercise Dru tests refused Disappearance of A V conduction disturbances after d training
7	M	Soccer	27	1 (PR 0 28)	–	–	Wenckebach during isoproterenol administration and exercise
8	M	Tennis	14	Wenckebach	16	1 (PR 0 18 to 0 28)	MVP AHB after EP Probable dual A V nodal pathway Normalization of A V conduction after sympathetic maneuvers drugs, exercise AVD after atropine
9	M	Basketball	18	1 (PR 0.28)	23¼	Wenckebach	MVP Normalization of A V conduction after sympathetic maneuvers drugs exercise
10	M	Cycling	15	Wenckebach, VPB	21	Wenckebach VPB	MVP Normalization of A V conduction after sympathetic maneuvers drugs exercise AVD after atropine Exercise abolished VPB

Abbreviations 1 = first degree A V block AHB = advanced heart block AVD = atrioventricular dissociation EAR = ectopic atrial rhythm EP = eyeball pressure MVP = mitral valve prolapse VPB = ventricular premature beats Wenckebach = second-degree A V block, Wenckebach type (Mobitz I)

was documented in the youngest athlete (Case 5) at the age of 13¼ years after 4 years of competitive activity and in the oldest one (Case 7) at the age of 27 years after he had practiced his sport for 9 years

Previous ECGs of six cases (Nos 2 5 6 8 9 and 10) were available They dated from a maximum of 6 years (Case 10) to a minimum of 15 months (Case 6) The first ECG showed the spontaneous occurrence of Wenckebach second degree A V block in Cases 5 6 8 and 10 first degree A V block (PR 0 28 sec) in Case 9, and normal A V conduction in Case 2 (PR 0 16)

Subsequent ECGs evidenced remarkable vari

Clinical communications

Wenckebach second degree A-V block in top ranking athletes: an old problem revisited

Paolo Zeppilli, M.D.*
Riccardo Fenici, M.D.
Massimo Sassara, M.D.
Marco Maria Pirrami, M.D.
Giovanni Caselli, M.D.**
Rome, Italy

Athlete's ECGs represent a major problem for many cardiologists and sports physicians, as in some cases the tracings significantly differ from those of normal untrained persons and sometimes closely resemble pathological ECG patterns like ventricular hypertrophy[1-4] and ST-T wave ischemic changes.[5-7] These findings have been attributed to the anatomical and physiological cardiac adaptations to heavy prolonged training, mainly of the endurance type. Particularly, sinus bradycardia, bradyarrhythmias, and first degree A-V block have been attributed to the absolute or relative increase of resting vagal tone following training, and therefore these have been regarded as "physiological" phenomena.

Wenckebach second degree A-V block is a very uncommon finding in normal people, but is significantly more frequent in young athletes, physically active middle aged persons, and is surprisingly frequent in horses.

Notwithstanding, these epidemiological data have not solved the central question if a vagogenic mechanism by itself can be entirely responsible for these anomalies. The nightly occurrence of second degree A-V block of Wenckebach type in clinically normal students seems to support the opinion that purely functional A-V conduction disturbances may occur. On the other hand, this reassuring view has been recently questioned by Young and associates, as they observed in seven out of 16 adolescents and young adults the progressive worsening of A-V conduction up to fixed complete heart block.

In order to ascertain the organic or functional nature of conduction disturbances in athletes, invasive electrophysiological investigations could be performed. However, as the large majority of athletes who undergo cardiological examination are clinically asymptomatic and fit, we believe it ethically correct to attempt only a noninvasive evaluation of conduction abnormalities in these athletes and to refer to invasive electrophysiological studies only those athletes with abnormal responses.

Since 1977 we began to submit all athletes with major A-V conduction disturbances to a noninvasive protocol study consisting of reflex autonomic tests, autonomic drug administration, and physical exercise. The present paper reports the results of such a diagnostic approach performed in a group of 10 top ranking athletes with Wenckebach type (Mobitz I) second-degree A-V block.

Material and methods

Ten males, 15 to 27 years old, were referred to us by the Physicians of Sports Medicine Institute of Rome because of the spontaneous or induced occurrence of Wenckebach second-degree A-V block on the ECG during a routine medical evaluation for sports aptitude. They practiced different sports, mostly of an endurance type (Table I). Wenckebach second degree A-V block

From the Medical Pathology Institute, Catholic University, Rome, and the Sports Medicine Institute, Rome, Italy.
Received for publication Sept. 6, 1979.
Accepted for publication Jan. 10, 1980.
Reprint requests: Paolo Zeppilli, M.D., Medical Pathology Institute, General Hospital A. Gemelli, Largo Gemelli 8, 00168 Rome, Italy.
*Medical Pathology Institute, Catholic University, Rome.
**Sports Medicine Institute, Rome.

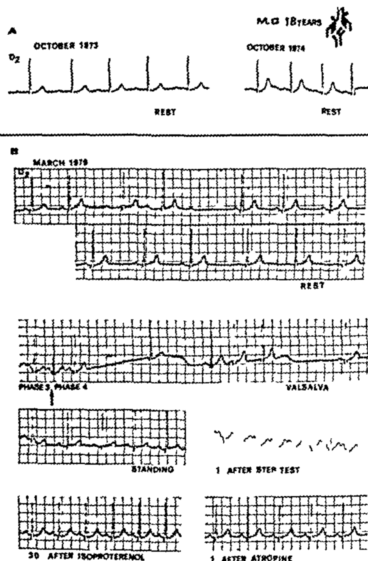


Fig 2 Case 9 Professional basketball player Mitral valve prolapse 4 First control tracing after 4 years of sports activity ECG evidences first-degree A V block (PR 0.28 sec) One year later a normal A V conduction pattern is observed *B* Last control tracing in March 19 9 (at age 24 years) Wenckebach type A V block normalized by Standing exercise isoproterenol and atropine administration Valsal a phase 4 induces sinus arrest with junctional escape beats and atrial premature beats

diograph at a paper speed of 25 mm /sec Subsequently all subjects were submitted to the following maneuvers

1 Eyeball pressure (EP) right (RCSP) and left carotid sinus pressure (LCSP)

2 Graded Valsalva maneuver (Valsalva) using a sphygmomanometer bl wn up to 40 mm Hg for as long as possible

3 Rapid open hyperventilation (ROHV) for at least 30 second

4 Rapid st ding ...

ECG recordi w ... onds before was continued th ... done for 10 seconds after e ...

Basal tracings were analyzed for (1) type of rhythm and sinus rate in beats/minute (b/min) by averaging 5 P P intervals and (2) A V conduction pattern

The effects of reflex tests on S A and A V nodes were evaluated (1) by measuring the maximum and minimum sinus rate achieved during and after each test and by checking for the possible occurrence of a shifting of the atrial pacemaker sinus arrest, or S A block (2) by observing if any change in A V conduction occurred

Pharmacological tests First a bolus of isoproterenol 5 mcg × 70 kg /body weight (BW) was administered intravenously under continuous

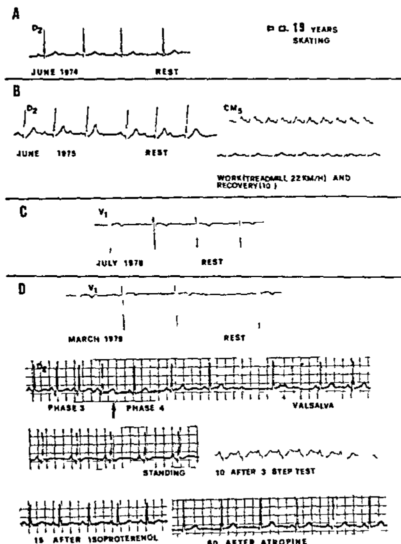


Fig 1 Case 2 World ranking skater *A* First control tracing after 3 years of sports activity normal ECG at rest *B* One year later Wenckebach phenomenon at rest is observed A V conduction is completely normalized during exercise *C* Three years later Wenckebach A V block is not appreciable *D* March 1979 Wenckebach A V block at rest A V conduction is normalized by Standing exercise isoproterenol and atropine administration Valsalva phase 4 induces an abrupt appearance of Wenckebach second degree A V block without a significant reflex sinus bradycardia There is transient shifting of the atrial pacemaker after atropine

ability of A V conduction pattern (Figs 1 to 3) mainly in relation to the intensity of training but the progression to advanced or fixed complete heart block has never been documented

All athletes at the time of our investigation were well trained and were completely asymptomatic Family and personal histories were accurately taken Furthermore since athletes are frequently motivated to minimize their symptoms whenever possible we tried to obtain the athletic history from their coaches Physical examination echocardiogram and phonocardiogram were taken in all subjects Echocardiographic findings diagnostic of mitral valve prolapse (MVP)[23, 8] were present in Cases 8 9 and 10 Cases 9 and 10 additionally had a variable mid systolic click Despite repeated auscultations no murmurs or clicks were found in Case 8 (silent prolapse)[29] None of these athletes had physical features characteristic of Marfan s syndrome[30] even if Patient No 9 was 6 feet tall

Reflex autonomic tests After informed consent to protocol study had been obtained in all athletes a basal standard ECG was recorded after 15 minutes rest in the recumbent position with a multichannel Hewlett Packard electrocar

Table II Effects on S A and A V nodes function of reflex autonomic tests drugs exercise

Case	Control ECG	Vagal maneuvers	Valsalva Phase 2 3	Valsalva Phase 4	ROHV	Stand	Isoproterenol	Atropine	Exerc
1	SR 68† Wenckebach	66 Wenckebach	95 0 22‡	69 Wenckebach	124 0 16	92 0 17	94 0 20	AVD 86 0 16	18 0 16
2	SR 55 Wenckebach	47 Wenckebach	100 0 12	75 Wenckebach	100 0 18	65 0 20	94 0 14	94 EAR 0 14	19 0 16
3	SR 62 1 (PR 0 24 to 0 36)	60 Wenckebach	100 0 16	62 1° (PR 0 24)	107 0 16	75 0 22	88 0 16	100 0 16	180 0 14
4	SR 55 Wenckebach	43 Dual A V node path way	79 0 24	58 Wenckebach	100 0 22	67 0 24	76 0 20	70 0.20	184 0 20
5	SR 75 1 (PR 0.24 to 0.36)	65 1 (PR 0 36)	88 0 16	SA 75 1 (PR 0 20)	115 0 14	75 0 20	96 0 16	96 0 15	18 0 14
6	SR 60 EAR Wenckebach	49 EAR Wenckebach	71 0 20	43 Wenckebach	88 0 22	52 0 20	– –	– –	190 0 16
7	SR 83 1 (PR 0 28)	80 1 (PR 0 26)	98 0 24	90 1 (PR 0 26)	120 0 22	100 0 22	105 Wenckebach	124 0 18	1 6 Wencke-bach
8 MVP	SR 60 1 (PR 0 18 to 0 28)	58 AHB dual A V node pathway	100 0 14	75 PR 0 16	100 0 14	65 0 14	94 0 16	AVD 90 0 14	187 0 16
9 MVP	SR 74 Wenckebach	67 Wenckebach	120 0 12	SA 45 PR 0 14	105 0 18	100 0 18	95 0 18	90 0 16	157 0 16
10 MVP	SR 66 Wenckebach VPB	58 Wenckebach	88 0.16	60 Wenckebach	100 0 20	70 0 20	– –	AVD 90 0 16	187 0 16

†Sinus rate beats/minute
‡PR interval duration-seconds.
Abbreviations 1 = first degree A V block AHB = advanced heart block AVD = atrioventricular dissociation EAR = ectopic atrial rhythm MVP = mitral valve prolapse ROHV = rapid open hyperventilation SA = sinus arrest SR = sinus rhythm Stand. = standing up VPB = ventricular premature beats Wenckebach = second-degree A V block, Wenckebach type (Mobitz I)

In assessing an abnormal sinus node function the following experimental criteria were utilized

1 A sinus arrest lasting more than 3 seconds after vagal maneuvers

2 An inadequate sinus rate increase after physical exercise

3 Isoproterenol test

a A sinus rate increase of less than 20 b/minute

b A shifting of the atrial pacemaker or emergence of a junctional rhythm

4 Atropine test[31, 3]

a A percent shortening of the basal sinus cycle length of less than 30%

b A target rate of less than 90 b/minute

c A heart rate increase sustained by non sinusal pacemakers

In assessing an abnormal atrioventricular node function the following criteria were uti

Fig 4 Case 1 ... ational juvenile team Mitral valve prolapse First control tracing January 19 6
Wenckebach type ... Two years later first degree A V block at rest with concertina like variation of
PR interval A ... block induced by eyeball pressure Probable dual pattern of A V conduction is
evid ... d sinus pressure as indicated by a progressive or abrupt lengthening of the PR
inter ... A V conduction C Atropine administration transient A V dissociation due to
accele ... llowed by normalization of A V conduction D Normal A V conduction during
work

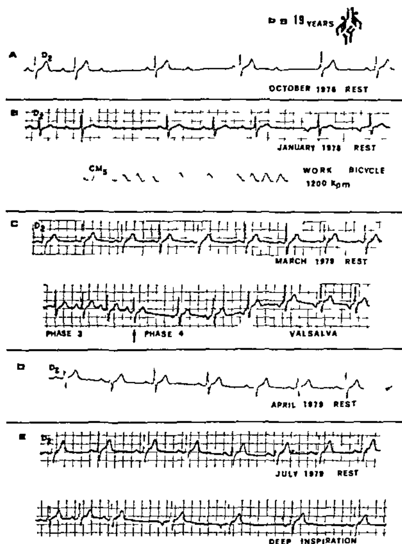


Fig 3 Case 6 Professional basketball player *A* First control tracing after 6 years of sports activity Wenckebach type block is evident *B* Fifteen months later Wenckebach A V block and spontaneous shifting of the atrial pacemaker is observed Exercise completely normalized the A V conduction *C* Last control tracing one month after forced detraining because of an ankle trauma ECG at rest shows normal A V conduction (PR 0 20 sec) Shifting of the atrial pacemaker during Valsalva phase 4 is appreciable *D* and *E* two and 5 months later (still inactive) normal A V conduction Abrupt change of the atrial pacemaker is induced by deep inspiration

ECG recording until the control heart rate was resumed (usually after 5 to 10 minutes) At least 15 minutes after the isoproterenol test atropine sulphate in a single dose of 0 02 mg /kg /BW was administered intravenously within 30 seconds The ECG was recorded continuously until a stable maximum sinus rate was achieved and then at the fifth tenth fifteenth and twentieth minute after the drug infusion The isoproterenol test was not performed in Case 10 because of ventricular premature beats at rest Subject No 6 refused pharmacological tests

Exercise *On the following day* the athletes were submitted to stress tests consisting of a 3 minute Step Test and after an adequate recovery a maximal continuous multistage exercise test on a bycicle or treadmill ergometer The maximum and total workload sustained the maximum heart rate and the O consumption (VO$_2$ max) were measured The ECG was monitored during and after effort (usually using a CM lead) for an accurate analysis of any A V conduction modification ST and T wave changes and the occurrence of arrhythmias

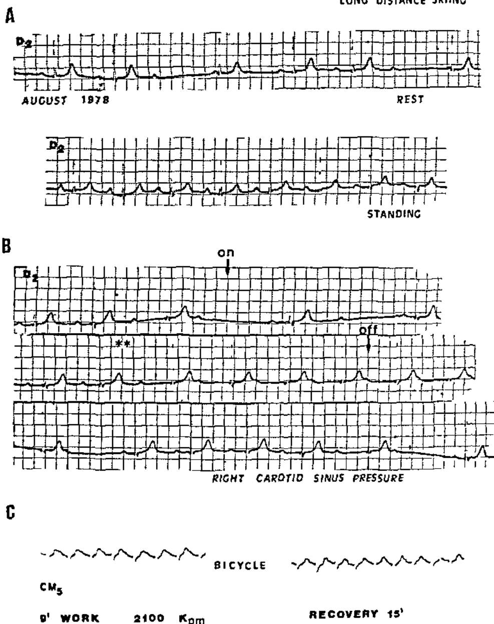


Fig 5 Case 4 Olympic ranking long distance skier *A* Wenckebach second degree A V block at rest with junctional escape beats Standing First degree A V block (PR 0.24 sec) is still present *B* Right carotid sinus pressure probable dual pattern of nodal A V conduction with evolution from Wenckebach phenomenon (*of fast pathway*) to 1 1 conduction with markedly prolonged PR interval (0 60 sec slow pathway) *C* Normal A V conduction during work

lized (1) an occurrence of A V conduction worsening during sympathetic stimulations or parasympathetic *inhibition or exercise and (2) the* absence of normalization of basal A V conduction disturbances during the same tests

Results (Table II)

Reflex autonomic tests Vagal maneuvers induced significant slowing of sinus rate in six cases (Nos 2 4 5 6 9 and 10) and had minimal or no effects in the remaining four In Case 8 EP *caused a high degree A V block* (Fig 4)

RCSP and LCSP induced an abrupt or progressive remarkable lengthening of PR interval with maintenance of 1 1 nodal A V conduction in Cases 4 and 8 suggesting a dual pattern of nodal A V conduction[11,12] (Figs 4 and 5) Sinus node response to Valsalva followed a *physiological*

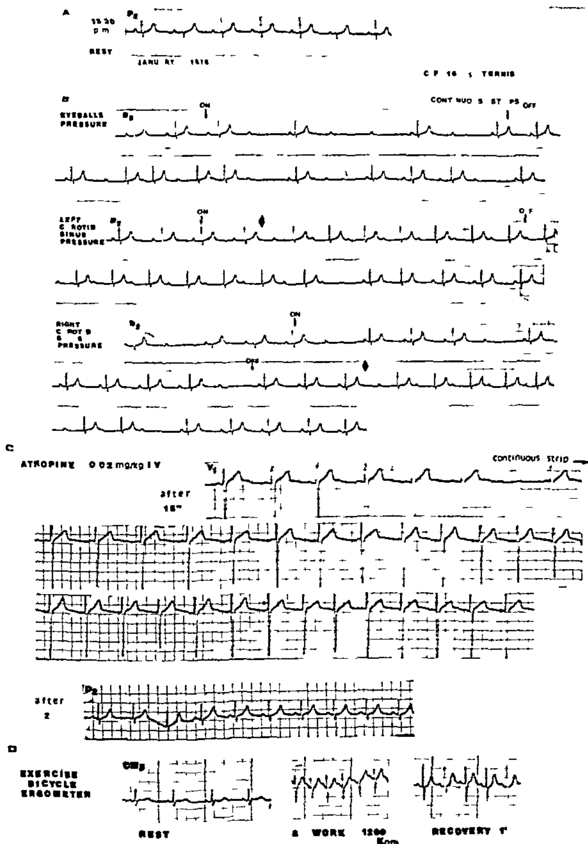


Fig 4 For legend see facing page

of sinus node to Standing was quite variable ROHV and/or Standing normalized A V conduction in eight cases (Nos 1 2 3 5 6 8 9 and 10) and improved it in Cases 4 and 7

Pharmacological tests Isoproterenol induced the expected increase of sinus rate in all cases This drug normalized A V conduction in all cases except one (Case 7 Fig 6) in which a Wenckebach A V block arose when sinus rate reached 90 b/minute In Case 4 a reduced response of sinus node to atropine was observed because of a target rate of less than 90 b/minute and a percent shortening of basal sinus cycle length inferior to 30%

Atropine induced a transient shift of the atrial pacemaker in Case 2 (Fig 1) and the occurrence of an accelerated junctional rhythm with complete or incomplete atrioventricular dissociation in Cases 1 8 and 10 (Fig 4) Sinus node response to atropine was within normal limits in the remaining five cases Atropine normalized A V conduction in all cases (Figs 1 to 6)

Exercise All athletes achieved the maximal age predicted heart rate in response to the highest workloads The physical performance of each of our athletes was adequate to his degree of training (Case 10 sustained a maximum workload of 2300 Kpm —375 Watts—on the bicycle) VO max values were over 45 ml /kg /min in all cases with a peak value of 71 ml /Kg /min in Case 3

None of the subjects showed ST and T wave abnormalities and arrhythmias during effort Exercise induced the complete disappearance of ventricular premature beats even at low work loads in Case 10

Work normalized A V conduction in all subjects except one (Case 7 Fig 6) in whom a transient Wenckebach phenomenon of nodal conduction was observed at a heart rate of 125 beats/minute

Follow up studies Case 8 was seen again 11 months after the study when he was still well trained ECG at rest was unchanged and A V conduction anomalies immediately and completely disappeared after sympathetic reflex stimulations and exercise Case 6 (Fig 3) was seen again in March 1979 1[illegible] months after our study when he had been inactive for [illegible] month because of an ankle trauma [illegible] at rest evidenced a 1 1 A V conduction [illegible] normal PR duration which was not influenced [illegible] reflex vagal stimulations

Valsalva phase 4 induced an abrupt change of the atrial pacemaker The last control examination in July 1979 after 5 months of inactivity confirmed the complete disappearance of A V conduction abnormalities and the persistence of an induced shift of the atrial pacemaker

Discussion

The introduction of intracardiac electrophysiological investigations has allowed a precise localization of sites of A V conduction disturbances and a better definition of the prognosis of different types of A V blocks[23] [4] On this regard the occurrence of Wenckebach second degree A V block in apparently normal persons [1] and in trained athletes [14] has been regarded as a vagally mediated functional disturbance of impulse conduction localized to the A V node and considered a benign clinical event

Unfortunately this optimistic view has been recently questioned by Young and associates[7] who found the possible evolution of Wenckebach type second degree A V block to advanced or complete block in adolescents without clinical *findings of cardiac disease* Those authors also pointed out that neither a positive response to exercise and atropine nor the results of the electrophysiological investigations can be considered reliable prognostic indexes However Hanne-Paparo and co workers[16] described a case of a 30 year old sportsman with Wenckebach A V block who had been followed for 10 years without evidence of progressive deterioration of A V conduction

More recently Murayama and associates,[2] showed that ECG changes observed in 102 Japanese olympic ranking athletes (Tokio Olympic Games 1964) during the competitive period (including first and second degree A V block) completely disappeared in 95% of subjects within 4 years from the end of physical activity

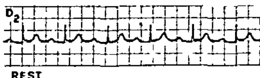
Our study seems to be in full agreement with the observations of Hanne Paparo and colleagues and Murayama and associates for the following reasons

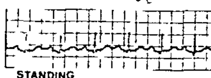
1 The favorable follow up studies of six of our athletes

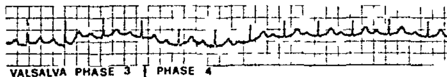
2 The characteristic spontaneous variability of A V conduction pattern in relation to the intensity of training or forced *detraining* (Figs 1 2 and 3)

MAY 1979 D V 27 YEARS















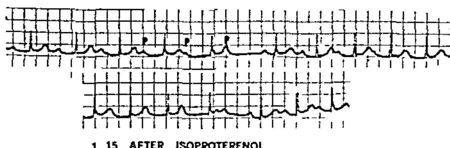


Fig 6 Case 7 Professional soccer player First-degree A V block at rest Worsening of A V conduction up to Wenckebach second-degree A V block after Step Test and isoproterenol administration After atropine 1 1 A V conduction with a PR interval of 0 18 sec is observed

behavior[11] in Cases 6 and 10 Valsalva phase 4 induced a sinus arrest of 1 8 seconds followed by junctional escape beats and premature atrial beats in Case 9 (Fig 2) in Case 5 a short period of sinus arrest interrupted by a single junctional escape beat and followed by regular sinus rhythm was observed The remaining six cases (Nos 1 2 3 4 7 and 8) did not show any slowing of sinus rate during Valsalva phase 4 (Figs 1 and 6) Valsalva phase 4 induced a Wenckebach type second degree A V block in Cases 1 and 2 (Fig 1)

Valsalva phase 2 and 3 completely normalized A V conduction in seven cases (Nos. 2 3 5 6 8 9 and 10) (Fig 1 to 3) in Cases 1 and 4 (Fig 5) it improved Wenckebach second degree block to first degree block while it caused only a small shortening of PR interval duration in Case 7 (Fig 6) An adequate increase of sinus rate during ROHV was observed in all subjects The response

block does not seem indicated provided that

1 They are asymptomatic

2 A complete noninvasive cardiological examination shows the absence of any cardiac pathological involvement

3 An immediate normalization of A V conduction pattern can be obtained with reflex sympathetic stimulations sympathomimetic or vagolytic drugs and physical exercise

Wenckebach second degree A V block in asymptomatic athletes with MVP features probably does not affect the prognosis if normal responses to the aforesaid provocative tests are observed

Summary

The occurrence of Wenckebach second degree (Mobitz I) A V block in apparently normal persons still provides a puzzle for the cardiologist as the benign nature of this event has been recently questioned This problem becomes more intriguing when Wenckebach A V block is encountered in asymptomatic top ranking athletes, because of medico legal implications We report 10 cases of highly trained athletes including three with mitral valve prolapse (MVP) features with a spontaneous or induced Wenckebach second degree A V block

Previous ECGs of six subjects dating from a maximum of 6 years to a minimum of 18 months were available Deterioration of A V conduction has never been documented and all six cases have remained asymptomatic for the whole follow up period

Athletes have been submitted to a protocol study consisting of ECG recording at rest during and after vagal and sympathetic reflex maneuvers drug administration (isoproterenol and atropine) submaximal and maximal exercise

Nine subjects have been considered to have normal responses of the A V node to provocative tests since conduction disturbances were improved or normalized by reflex sympathetic stimulations and were completely normalized by autonomic drug administration and exercise

One athlete showed abnormal responses to tests In ord[illegible]ive a conclusive prognostic and medico leg[illegible]ment we advised him to submit to a[illegible] electrophysiological investigation

Wenck[illegible]ond degree A V block in athletes may be a more common finding than so far described, especially when a systematic search is made In our opinion this event can still be considered a vagally induced benign feature of athlete s heart provided that an immediate improvement of A V conduction is obtained in response to reflex sympathetic maneuvers and that a complete normalization after sympathomimetic and vagolytic drug administration and physical exercise is observed

The clinical histories of our athletes and the observed complete disappearance of conduction disturbances after detraining strongly support this opinion

Wenckebach second degree A V block in asymptomatic athletes with MVP features probably does not affect the prognosis if similar favorable responses to the aforesaid tests are observed

We are grateful to Dr Antonio Greco for providing facilities and continuous encouragement in our studies We also thank Prof Antonio Venerando for his scientific assistance in processing the manuscript and Mr G Madeddu for his secretarial assistance We are additionally indebted to Dr Sima Sandric Dr Fernando Cecchetti and Dr Antonio Spataro for their help in evaluating the athletes

REFERENCES

1 Hanne Paparo N Drory Y Schoenfeld Y Shapira Y and Kellerman J Common ECG changes in athletes Cardiology **61** 267 1976

2 Lichtman J O Rourke A Klein A and Karliner J Electrocardiogram of the athlete Arch Intern Med **132** 763 1973

3 Venerando A Caselli G Piovano G and Rossi F Semeiotica cardiologica in medicina dello sport Med Sport **30** 25 1977

4 Zeppilli P Sandric S Cecchetti F Spataro A Anselone G and Assorgi G QRS voltage criteria in the assessment of right and left ventricular enlargement in athletes comparative ECG VCG and echocardiographic study XXI World Congress in Sports Medicine Brasilia September 1978 (In press)

5 Hanne Paparo N Wendkos M H and Brunner D T wave abnormalities in electrocardiograms of top-ranking athletes without demonstrable organic heart disease Am Heart J **81** 743 1971

6 Zeppilli P Sandric S Caselli G Spataro A and Assorgi C Comparative electrocardiographic study in athletes with ST T wave anormalities Sports Cardiology Bologna 1980 Aulo Gaggi p 735

7 Zeppilli P., Pirrami M M Sassara M and Fenici R T wave abnormalities in top-ranking athletes effects of isoproterenol atropine and physical exercise Am Heart J **100** 213 1980

8 Baader H S Cardiovascular adaptations in the trained athlete Sports Cardiology Bologna 1980 Aulo Gaggi p 3

9 Johnson R L Averill K H and Lamb L E Electrocardiographic findings in 67 375 asymptomatic individuals VII A V block Am J Cardiol **6** 153 1960

3 The significant improvement of A V conduction obtained even after simple sympathetic maneuvers and the complete normalization induced by autonomic drug administration and exercise in all athletes except one

Nevertheless abnormal responses of A V nodal conduction to isoproterenol and exercise were appreciable in Case 7 (Fig 6) In order to obtain a conclusive prognostic and medico legal assessment we advised this athlete to submit to an invasive electrophysiological investigation which up to now he has refused

Functional vagogenic depression of A V nodal conduction in athletes seems therefore confirmed by our observations However a hyporeactivity of sinus node to vagal maneuvers as evidenced by the lack of significant reflex sinus bradycardia during Valsalva phase 4 and abnormal responses of sinus node to atropine administration have been observed in five cases (Nos 1 2 4 8 and 10, Figs 1 and 4) These events could suggest the possibility of sinus node dysfunction or sick sinus syndrome (SSS)[3, 34]

Nevertheless similar behavior after atropine administration has been reported in apparently normal persons of different ages especially in young subjects and when low doses of the drug were employed[1] The effects of different doses of atropine on S A and A V nodes have been recently investigated by Das and colleagues S A node response was characteristically bimodal as sinus rate slowed at smaller doses and accelerated at higher doses while A V node showed acceleration of conduction whatever the dose of atropine administered

The above mentioned authors suggested that like any other receptor blocking agent[1] atropine can produce a transient stimulating effect namely a vagomimetic response Therefore the simultaneous occurrence of sinus bradycardia and A V conduction facilitation could be explained by the different electrophysiological effects of acetylcholine on the rates of impulse formation and impulse conduction Moreover the appropriate sinus rate increase after isoproterenol infusion[31, 3] and exercise[3] seems to confirm the normality of sinus node automaticity in our athletes Therefore despite the recent report of Roland and associates we strongly doubt that at present our athletes could be affected by SSS On the other hand in spite of our apparently reassuring opinion long term follow up studies are mandatory in order to verify the possible role of heavy prolonged training in the pathogenesis of SSS at a later time in life

It now remains to explain why

1 A training mediated increase of vagal tone has induced in our athletes major A V conduction disturbances instead of sinus bradycardia which is the usual autonomic response of the heart to training[3, 11] and

2 The hyporeactivity of the sinus node to Valsalva and atropine administration exists in some of our athletes

As our subjects did not show any evidence of chronic degenerative diseases involving the autonomic nervous system[4, 50] a possible alternative explanation of the aforesaid findings could be found in an individually different distribution of the parasympathetic influence on S A and A V nodes in otherwise normal persons

Wenckebach second degree A V block and mitral valve prolapse in athletes MVP may be an unexpected finding in asymptomatic top ranking athletes[6, 7, 51, 5] In accordance with the findings of Barlow[53, 5] we previously suggested that in the assessment of the sports aptitude of athletes with MVP features a permissive criterium has to be adopted provided that no ventricular tachyarrhythmias at rest[55, 5] and during effort[3] have been observed However remarkable sinus bradycardia with syncopal episodes[5] and atrioventricular and intraventricular conduction disturbances[8, 60] have been recently reported in subjects with MVP but their pathogenetic clinical and prognostic implications are still questionable

In the present report the S A and A V nodes responses to provocative tests and the follow up studies of athletes with MVP did not differ from the results in normal athletes

Therefore in our opinion the occurrence of A V conduction disturbances in asymptomatic athletes with MVP features has to be regarded in the same manner as in normal sportsmen provided that these anomalies have shown normal responses to the aforesaid protocol study

Conclusions

Our observations support the opinion that a systematic aggressive diagnostic approach in athletes with Wenckebach second degree A V

murmurs Emphasis on the billowing mitral leaflet syndrome AM HEART J 90 636 1975
52 Nevins M A Desser K B., and Benchimol, A Mitral valve prolapse in a professional basketball player Physicians Sports Med. January 109 1979
53 Barlow J B and Pocock W A Mitral valve prolapse the specific billowing mitral leaflet syndrome or an insignificant non-ejection systolic click? AM HEART J 97 277 1979
54 Barlow J B Personal communication
55 DeMaria A N., Amsterdam E A., Vismara L A et al The variable spectrum of rhythm disturbances in the mitral valve prolapse syndrome Circulation 49 and 50 (Suppl. III) 222 1974
56 Winkle R A Lopes, L G Fitzgerald J W Goodman D J Schroeder J S and Harrison D C Arrhythmias in patients with mitral valve prolapse Circulation 52
1975
57 Leichtman D Nelson R., Gobel F., Alexander C. and Cohn J N Bradycardia with mitral valve prolap
Ann Intern Med 85 453 1976
58 Rizzon P Antonelli G Biasco G Brindicci G and Biase M Chronic juvenile AV nodal dysfunction as ciated with mitral valve prolapse Eur J Cardiol. 6 589 1978
59 Chandraratna P N A Ribas-Menecier C Littman, B and Samet P Conduction disturbances in patie *with mitral valve prolapse* J Electrocardiol. 10(3) 2 1977
60 Schaal S F., Fontana M E and Wooley C Mit valve prolapse Spectrum of conduction defects a arrhythmias Circulation 49 97 1974 (Abstract)

Copyright Information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner s consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients This consent is given on the condition however that the copier pay the stated per copy fee through the Copyright Clearance Center Inc 21 Congress Street Salem Mass 01970 617 744 3350 for copying beyond that permitted by Sections 107 or 108 of the U S Copyright Law This consent does not extend to other kinds of copying such as copying for general distribution for advertising or promotional purposes for creating new collective works or for resale

10 Manning G W, and Sears G A Postural heart block Am J Cardiol 9 558 1962.
11 Fenici R, Caselli G Zeppilli P, and Piovano G High degree A V block in 17 well trained endurance athletes Sports Cardiology Bologna 1980 Aulo Gaggi p 523
12 Meytes, I Kaplinsky E Yahini J H Hanne Paparo N and Neufeld H N Wenckebach A V block A frequent feature following heavy physical training Am HEART J 90 426 1975
13 Sargin O Alp C Tansi C and Karaca L Wenckebach phenomenon with nodal and ventricular escape in marathon runners Chest 57 1 1970
14 Smith W G Cullen K J and Thorburn I O ECGs of marathon runners in 1962 Commonwealth Games Br Heart J 26 469 1964
15 Tomasini, M Wenckebach period in a young athlete Med Lavoro 57 614 1966
16 Cullen K and Collin R Daily running causing Wenckebach heart block Lancet 2 729 1964
17 Grimby G and Saltin B Letter to the Editor Lancet 2 962 1964
18 Buchanan J W Spontaneous arrhythmias and conduction disturbances in domestic animals Ann N Y Acad Sci 127 224 1965
19 Brodsky M Wu D, Denes P Kanakis C and Rosen K M Arrhythmias documented by 24 hour continuous electrocardiographic monitoring in 50 male medical students without apparent heart disease Am J Cardiol 39 390 1977
20 Lighfoot P R Sasse L Mandel W G and Hayakawa J HIS bundle electrograms in healthy adolescents with persistent second degree A V block Chest 63 358 1973
21 Young D Eisenberg R Fish B and Fisher J D Wenckebach atrioventricular block (Mobitz I) in children and adolescents Am J Cardiol 40 393 1977
22 Scherlag B J Lau S H Helfant R H Berkowitz W D Stein E and Damato A N Catheter technique for recording His bundle activity in man Circulation 39 13 1969
23 Damato A N Lau S H Helfant R H Stein E Patton R D Scherlag B J and Berkowitz W D A study of heart block in man using His bundle recordings Circulation 39 297 1969
24 Damato A N, and Lau S H Clinical study of the electrogram of the conducting system Progr Cardiovasc Dis 13 119 1970
25 De Maria A N King J F Bogren H G Lies J E and Mason, D T The variable spectrum of echocardiographic manifestations of mitral valve prolapse syndrome Circulation 50 33 1974
26 Markiewicz W Stoner T London E Hunt S A and Popp R L Mitral valve prolapse in one hundred presumably healthy young females Circulation 53 464 1976
27 Sahn D J Wood J Allen H D Peoples W and Goldberg S J Echocardiographic spectrum of mitral valve motion in children with and without mitral valve prolapse the nature of false positive diagnosis Am J Cardiol 39 422 1977
28 Weiss A N Mimbs J W Ludbrook P A and Sobel B E Echocardiographic detection of mitral valve prolapse Exclusion of false positive diagnosis and determination of inheritance Circulation 52 1091 1975
29 De Maria A N and Mason D T Silent mitral prolapse Circulation 50 1284 1974
30 Pyeritz R E and McKusick V A The Marfan syndrome diagnosis and management N Engl J Med 300 772 1979
31 Gruppo Italiano di studio di elettrofisiologia delle aritmie Protocollo di studio della funzione del nodo del seno G Ital Cardiol 9 438 1979
32 Ferrer M I The sick sinus syndrome Circulation 47 635 1973
33 Dighton D H Sinus bradycardia Autonomic influences and clinical assessment Br Heart J 36 791 1974
34 Dighton D H Sinoatrial block Autonomic influences and clinical assessment Br Heart J 36 791 1974
35 Wit A L Weiss M B Berkowitz W D Rosen K M Steiner C and Damato A N Pattern of atrioventricular conduction in the human heart Circ Res 27 345 1970
36 Rosen K M, Metha A, and Miller R A Demonstration of dual atrioventricular nodal pathways in man Am J Cardiol 33 291 1974
37 Kalbfleisch J H Stowe D F and Smith J J Evaluation of the heart rate response to the Valsalva maneuver Am HEART J 95 707 1978
38 Hanne Paparo N Long term ECG monitoring of a sportsman with second degree A V block Sports Cardiology Bologna 1980 Aulo Gaggi p 559
39 Murayama M, and Kuroda Y Cardiovascular future of athletes Sports Cardiology Bologna 1980 Aulo Gaggi p 401
40 Gambetta M Denes P and Childers R W Vagally induced second degree A V block Mobitz type I and the hyporeactive SA node Chest 62 152 1972
41 Dauchot P and Gravenstein J S Effects of atropine on the electrocardiogram in different age group Clin Pharmacol Therap 12 274 1970
42 Cristallo E Amodio F Rizzo A, et al Paradoxical effect of atropine upon sinus node in normal persons Atti of the Fortieth Congress of the Italian Society of Cardiology Bari June 1979 page 117 (Abstract)
43 Das G Talmers F N and Weissler A M New observations on the effects of atropine on the sinoatrial and atrioventricular nodes in man Am J Cardiol 36 281 1975
44 Patton W O M The principles of drug action Proc R Soc Med 53 815 1960
45 Hoffman B F, and Cranefield P F Electrophysiology of the heart New York, 1960 McGraw Hill pages 108 114
46 Baily J C Greenspan K, Elizari M V Anderson G J and Fisch C Effects of acetylcholine on automaticity and conduction in the proximal position of the His Purkinje specialized conduction system of the dog Circ Res 30 210 1972
47 Holden W McAnulty J and Rahimtoola S Inadequate heart rate response to exercise in the sick sinus syndrome Circulation 53 and 54 (Suppl II) 146 October 1976 (Abstract)
48 Roland J M A Varghese P J Shematek J Pieroni D and Hopkins J Sinus node dysfunction in young athletes a possible cause of sudden death Circulation 51 and 52 (Suppl II) October 1975 (Abstract)
49 Amorin D S Mello de Oliveira J A Manco J C Gallo L Jr, and de Mello and Oliveira J S Chagas heart s disease First demonstrable correlation between neuronal degeneration and autonomic impairment Acta Cardiol 28 431 1973
50 Lloyd Mostyn R H and Watkins, P J Defective innervation of the heart in diabetic autonomic neuropathy Br Med J iii 15 1975
51 Barlow J B and Pocock W A The problem of nonejection systolic clicks and associated mitral systolic

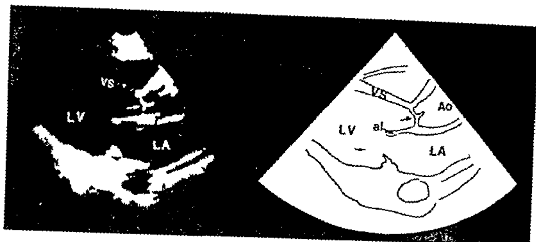


Fig 1 A left ventricular longitudinal cross sectional echocardiogram from a normal control depicting the left ventricle *(LV)* left atrium *(LA)* ventricular septum *(VS)* and the anterior leaflet of the mitral valve *(al)* *The white arrow s head* lies at the mouth of the aorta at the level of the aortic ring and points to the coaptation point (at mid aortic level) of the right and posterior aortic valve cusps in diastole The cusps lie well above the aortic ring

phases of the cardiac cycle were noted The coaptation point of the aortic cusps were analyzed for its degree of echo reflection and for its location and the presence of any diastolic motion M mode echocardiograms were analyzed for aortic root size location of the coaptation line in diastole echo reflectivity of the aortic cusps and for fluttering of the mitral and aortic valve leaflets

Study population A total of 112 consecutive patients with cross sectional echocardiographic criteria for mitral valve prolapse as previously described[13] were analyzed for morphological appearance and mobility of the aortic valve The longitudinal left ventricular cross sectional echocardiographic study was considered adequate for imaging the aortic valve only when two cusps were clearly seen and their motion and coaptation point could be visualized throughout diastole This demanded that the surrounding landmarks (the interventricular septum anterior mitral valve leaflet and aortic root) were well visualized M mode echocardiographic aortic root enlargement was considered present if the aortic root exceeded previously defined normal limits Cusp thickness was considered increased when one or both cusps reflected increased echoes from any part of the cusp compared to controls and from a target of known thickness in the same patient Downward displacement of the cusp tissue or coaptation point was assessed in real time and displacement was felt to be present when leaflet tissue or the coaptation point were imaged inferior to the aortic valve ring towa[rds] the left ventricular outflow tract Tricuspid v[alve] prolapse was defined using previously descri[bed] cross sectional echocardiographic criteria[11] [uti]lizing both the right ventricular longitudi[nal] inflow tract and apical views Severity of mit[ral] valve prolapse was determined using both l[eft] ventricular longitudinal and four chamber api[cal] views with severe mitral valve prolapse be[ing] present when the mitral leaflets moved w[ell] beyond the mitral ring level towards the l[eft] ventricular apex Mild prolapse was defined [as] minimal leaflet displacement beyond the mitr[al] valve ring and moderate was defined as bei[ng] between mild and severe

All studies were analyzed blindly by thre[e] echocardiographers on two different occasions The inter and intraobserver variability was les[s] than 5%

Results

Control population M mode echocardiographic aortic root measurement in 14 controls revealed normal aortic root size in all (mean 3 3 ± 0 3 cm [SD] range 2 8 to 3 8 cm) All subjects demonstrated the coaptation line of the two visualized aortic cusps in the center of the aortic root The two cusps appeared symmetrical with only a minimum of echo refractivity which established the normal degree of echo reflection Mitral valve fluttering (anterior leaflet) suggestive of aortic regurgitation was not seen in any of the control subjects and none of the 14 had any evidence of

Cross-sectional echocardiographic detection of aortic valve prolapse

T Joseph Mardelli M D *
Joel Morganroth M D
Masahito Naito M D
Chin C Chen M D
With the technical assistance of Linda Meixell R D.M S and Connie Parrotto
Philadelphia Pa

The identification of aortic valve prolapse has been limited to surgical and pathological studies[1-3] Read and Thal[1] in 1965 identified at surgery the coexistence of aortic valve prolapse in patients with mitral and tricuspid valve prolapse The mucoid degeneration in the aortic valve appeared to be due to a diffuse connective tissue disorder involving the cardiac fibrous skeleton unrelated to aging M mode echocardiography[4] has been able to document mitral and tricuspid valve prolapse in part because of the larger atrioventricular annular and leaflet size rendering easy identification of the prolapsing motion Conversely the aortic annulus is smaller and aortic cusps less voluminous and less echo reflective and thus previous noninvasive identification of aortic valve prolapse has not specifically been defined Chandraratna and colleagues[9] reported a single case of aortic valve prolapse demonstrated at surgery in which the M mode echocardiography revealed diastolic aortic leaflet fluttering Rippe and co workers reported four patients who had marked aortic valve excursions on M mode echocardiography and were thought therefore to have aortic valve prolapse These patients clinically did have aortic regurgitation and mitral valve prolapse and thus aortic valve prolapse syndrome was suggested Cross sectional echocardiography provides real time evaluation of the aortic valve and thus this study was conducted to determine the prevalence and characteristics of aortic valve prolapse as defined by this noninvasive technique

Material and methods

All cross sectional echocardiographic studies were obtained using a wide angle 84 degrees commercially available phased array system (Varian V 3000) with a transducer containing 32 mounted piezoelectric crystals with a diameter of 1 3 × 1 2 inches at the skin level All studies were recorded on videotape (Sanyo) and were later reviewed in real time slow motion and frame by frame analysis Individual frame selections for figures were photographed using a Polaroid camera The quality of these still frame images was significantly degraded since only one half of the line density was present during the still framing M mode echocardiographic studies were obtained using a Smith Kline Echoline 20A with a 2 25 MHz transducer Left ventricular longitudinal and short axis views of the aortic valve were obtained using the conventional approach[12]

Control population Fourteen subjects (mean age 51 ± 10 years [SD]) with normal cardiac catheterization and cineangiographic findings were selected to define normal aortic valve morphology and motion characteristics by cross sectional echocardiography The thickness of the aortic cusps and their mobility during various

From th Departments f Medicin and Rese h The La k au Hosp t l, and the D partm nt of Medi ine of th Jeff rso Medic l School f The Thomas J ff rso U ersity Ph l delphia

Recei ed f r publi at n D c 17 1979

Accepted fo publ cat o Apr 4 1980

Reprint requests Joel Morganr th, M D C rdiovasc lar D vision The Lank nau Hosp tal Lancaste A West of City A e Ph lad l phia Pa 19151

* C rre t ddress S uth B ltim r C en ral Hosp tal Balt more Md.

000?-8 03/80/090?95 + 0 $00 0 0 © 1980 The C V Mo by Co

Table I Comparison of 60 patients with mitral valve prolapse (MVP) alone with 17 cases of both MVP and aortic valve prolapse (AVP)

N	*MVP* (60)	*AVP (+ MVP)* (17)
Mean age (±SD) in years	38 ± 18	36 ± 21
Mean aortic root systolic size (in cm ± SD) by M mode echocardiography	3 1 ± 0.3	3 5 ± 0.5
Aortic root enlargment by M mode echocardiography	0	6
Clinical aortic regurgitation	0	4
Tricuspid valve prolapse by cross-sectional echocardiography	31	16
Increased aortic cusp thickness by cross-sectional echocardiography	0	16

$p < 0 01$

mean age of 36 ± 21 (SD) years (11 were female) and revealed a different aortic valve morphology and motion characteristic compared to controls

Cross sectional echocardiographic findings In 16 of 17 patients the echo reflectivity from the aortic valve cusp tissue was considered increased compared to conrols The coaptation point of the aortic valve was considered eccentric by cross sectional echocardiographic analysis in six patients while the other 11 patients showed a central positioned coaptation point The six patients with eccentric coaptation all had three aortic valve cusps demonstrated on short axis tomographic view The eccentricity was noted to be anterior in four (Fig 2*A*) and posterior in two patients (Fig 2*B*) Real time motion assessment revealed that unlike the controls there was downward displacement of both aortic cusps during diastole in 13 of the 17 patients whereas two cases had isolated right or posterior cusp

Sixteen of 17 patients with aortic valve prolapse demonstrated evidence of tricuspid valve prolapse on the right ventricular longitudinal inflow tract and/or apical four chamber view The other case demonstrated a normal tricuspid valve but only an apical view was available In 31 (52%) of the 60 subjects with mitral valve prolapse but without aortic valve prolapse tricuspid valve prolapse was demonstrated (p = NS) Longitudinal left ventricular and apical views were used to assess the severity of mitral valve prolapse The severity of mitral valve prolapse in the 17 patients with aortic valve prolapse (six mild five moderate six severe) was not statistically different from that seen in the 60 cases with mitral valve prolapse without aortic valve prolapse

M mode echocardiographic and clinical findings There was no aortic root enlargement visualized by M mode echocardiography in any of the 60 patients with mitral valve prolapse without aortic valve prolapse mean aortic root diameter was 3 1 ± 0 3 cm (SD) Aortic root size was enlarged in six of 17 patients with aortic valve prolapse the mean for all 17 patients was 3 5 ± 0 5 cm (SD) Evidence of anterior mitral leaflet fluttering compatible with aortic regurgitation was seen in four of 17 and in three of the four physical examination revealed a diastolic murmur compatible with aortic insufficiency One patient had moderate aortic regurgitation by aortic root angiography with three aortic valve cusps Three of these four patients had evidence of aortic root enlargement on M mode echocardiography whereas three of 13 without aortic regurgitation showed aortic root dilatation Two of these four patients had diastolic aortic valve separation and fluttering as previously described [10] Two of the 17 patients had abnormal diastolic echoes from the prolapsed aortic valve protruding into the left ventricular outflow tract similar to that described by El Shahawy and co workers [16] Table I contrasts those patients with and without aortic valve prolapse

Discussion

This cross sectional echocardiographic study has suggested the presence of aortic valve prolapse in 17 (22%) of 77 patients with mitral valve prolapse Aortic valve morphology and motion characteristics were clearly altered in these 17 patients compared to a control population of normal subjects and to 60 patients (78%) of the group selected with mitral valve prolapse Unfortunately the striking real time echocardiographic findings noted in these patients cannot be reproduced on still photographies as used in the representative Figs 1 and 2 The 17 patients with aortic valve prolapse showed higher degrees of aortic valve thickening eccentricity of aortic cusps and a higher prevalence of clinical aortic regurgitation and M mode echocardiographic aortic root dilatation

Carter and co workers[3] have classified aortic

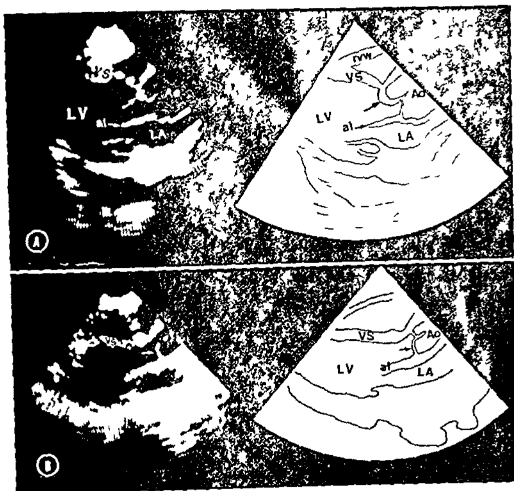


Fig 2 *A* A left ventricular longitudinal cross sectional echocardiogram from a patient with aortic valve prolapse demonstrating the left ventricle *(LV)* aorta *(Ao)* left atrium *(LA)* anterior mitral valve leaflet *(al)* and the right ventricular wall *(rvw)* *The head of the white arrow* lies well into the left ventricular outflow tract at mid mitral valve level and points to a marked prolapse and asymmetry of the right aortic valve cusp *B* A left ventricular longitudinal cross sectional echocardiogram from a patient with aortic valve prolapse demonstrating the left ventricle *(LV)* left atrium *(LA)* aorta *(Ao)* and the anterior mitral valve leaflet *(al)* *The white arrow* points to a prolapsed thickened and asymmetric large posterior aortic valve cusp

mitral valve prolapse Cross-sectional echocardiographic evaluation revealed a central coaptation point of the two aortic cusps and relatively faint echo reflection as viewed from the left ventricular longitudinal section Real time analysis of the aortic valve closure pattern in diastole with subsequent frame by frame analysis revealed that the coaptation point of the two cusps remained fixed throughout diastole and that there was no downward displacement towards the left ventricle during diastole The aortic cusps were slightly convex towards the center of the aorta at the level of their coaptation point Fig 1 demonstrates a typical example of a normal aortic valve closure pattern during diastole

Still photos demonstrated in this manuscript are limited to show the striking real time echocardiographic findings since the aortic valve cusps tended to be *relatively* poor echo reflectors and therefore their position was difficult to demonstrate when only one half of the line density was present on stop frame images

Study population The aortic valve was adequately visualized for analysis in 77 of 112 (68%) patients with cross sectional echocardiographic evidence of mitral valve prolapse Sixty (78%) of these 77 patients had a mean age of 38 ± 18 years (SD) and in all 60 the aortic valve characteristics and motion features were identical to those of the 14 controls These patients were considered to have mitral valve prolapse without aortic valve prolapse The remaining 17 patients (22%) had a

changes in patients with aortic valve prolapse is present Previously reported surgical experience[1, 17] suggests that a subgroup of cases exists with aortic mitral and tricuspid valve prolapse in which valvular regurgitation may require prosthetic valvular replacement

The inability of M mode echocardiography to visualize and detect superoinferior prolapsing motion of aortic valve produces serious limitation for this technique in the detection of aortic valve prolapse However few features on M mode echocardiographic tracings may suggest the presence of aortic valve prolapse The presence of increased aortic valve reflections eccentricity of the diastolic closure line aortic root enlargement abnormal diastolic echoes in the left ventricular outflow tract and the presence of fluttering of the anterior mitral leaflet can all be used to suggest the possibility of coexistence of aortic valve prolapse in patients with mitral valve prolapse

The limitations of this cross sectional echocardiographic study are clear First the true prevalence of adequate visualization of the aortic valve cannot be assessed from this study since it was performed in a retrospective manner in selected patients with mitral valve prolapse referred to our echocardiographic laboratory, and thus may not be applicable to population studies in patients without mitral valve prolapse Second the analysis of a study populaton of mitral valve prolapse for the detection of aortic valve prolapse may create bias as to the actual spectrum of aortic valve prolapse The possibility of the presence of aortic valve prolapse without mitral valve prolapse cannot be excluded from this study In addition we have no data comparing the actual clinical manifestations and natural history of patients with aortic valve prolapse compared to those patients with mitral valve prolapse without aortic valve prolapse Nevertheless this study demonstrates the potential of cross sectional echocardiography to diagnose a subgroup of patients with mitral valve prolapse with specific aortic valvular abnormalities suggesting the coexistence of aortic valve prolapse The potential of evaluating the prevalence of aortic valve prolapse in a populaton with aortic insufficiency has not yet been explored

Summary

To determine the potential for cross sectional echocardiography to define aortic valve prolapse 14 controls with a mean age of 51 ± 10 years (SD) with normal cardiac catheterization were studied by cross sectional echocardiographic left ventricular longitudinal and short axis views to define normal aortic valve morphology and motion characteristics Similarly, 112 patients with cross sectional echocardiographic mitral valve prolapse were analyzed to determine aortic valve morphology and motion characteristics In all 14 controls the left ventricular longitudinal view revealed the aortic valve as a faint echo reflector with symmetrical cusps whose closure point as well as the cusp tissue itself did not display any downward (or prolapsing) motion toward the left ventricular outflow tract In the group of 112 patients with mitral valve prolapse, the aortic valve was successfully imaged for detailed analysis in 77 Sixty of these 77 (78%) had a mean age of 38 ± 18 years (SD) and revealed aortic valve morphology motion characteristics similar to controls All of the remaining 17 patients (mean age 36 ± 21 years 11 female) revealed a downward displacement (or prolapse) of the aortic valve during diastole There was an increased echo reflection from the cusp tissue in 16 of 17 and in six of 17 cusp size was asymmetric producing eccentricity of the coaptation point All six of these had three aortic cusps seen on the short axis view The aortic root size was normal in all controls in the 60 patients with mitral valve prolapse without aortic valve prolapse whereas six of 17 patients with aortic valve prolapse had aortic root enlargement When comparing the group with (N = 17) and without (N = 60) aortic valve prolapse the tricuspid valve was prolapsed in 16 of 17 compared to 31 of 60 (p = NS) and aortic insufficiency was present in four of 17 compared to none of 60 ($p \leq 0.01$)

In conclusion cross sectional echocardiography can identify a subset of patients with mitral valve prolapse who have aortic valve prolapse in which aortic root dilatation and aortic regurgitation may be encountered Such patients may reflect a more diffuse myxomatous degeneration of the cardiac skeleton

REFERENCES

1 Read R C and Thal A P Surgical experience with symptomatic myxomatous valvular transformaton (the floppy valve syndrome) Surgery 59 173 1966
2. Frable W J Mucinous degeneration of the cardiac valves. The "floppy valve syndrome J Thorac Cardiovasc Surg 58 62 1969
3 Carter J B., Sethi S Lee G B and Edwards J F

valvular prolapse into etiologies associated with intact cusps, ruptured cusps, loss of commissural support, and ventricular septal defect with displacement of the aortic root. The patients in our study all had intact cusps as defined by echocardiography since none had evidence of serious cardiovascular disease such as dissecting aortic aneurysm, ventricular septal defect, or traumatic or infected aortic valve or aorta. Causes of intact cusps with aortic valve prolapse include (1) intrinsic weakness due to "floppy valve syndrome" with or without dilatation of the aorta, (2) fraying of a cusp[1] characterized by thinning without through and through laceration which may result in the affected cusp ballooning in an aneurysm-like faction towards the ventricle, and (3) excessive aortic valve tissue in patients with a congenital bicuspid aortic valve.[3]

Pathologic and surgical evidence of aortic valve prolapse due to "floppy valve syndrome" has been suggested.[1,3,11,16] Read and colleagues[1] in 1965 reported the existence on histology of myxomatous transformation of the cardiac valves in surgical patients and suggested the term "floppy valve syndrome." These patients, they suggested, may represent a possible forme fruste of Marfan's syndrome. No specific etiologic basis was identified. Seven cases of aortic valve prolapse were defined surgically by Frable,[2] and McKay and Yacoub[17] reported that 9% of 560 patients who underwent mitral or aortic valve replacement had myxomatous degeneration of the mitral and/or aortic valve. Eleven had isolated aortic valve prolapse and nine of these were men.

Previous echocardiographic studies[9, 6] to define aortic valve prolapse have been limited to M mode technique and none could be considered diagnostic or specific for aortic valve prolapse. Real time visualization of the aortic valve using cross sectional echocardiography in which a superoinferior direction of the aortic valve can be analyzed is required to establish this diagnosis noninvasively. Due to the relatively small aortic ring and cusps area, cross-sectional echocardiographic analysis to detect aortic valve prolapse requires meticulous review of the real time study. The redundancy of a cusp with diastolic motion towards the left ventricular outflow tract has been our operational definition of aortic valve prolapse. The sensitivity and specificity of this technique cannot be evaluated due to the lack of a "gold standard" for prolapse valves, but we believe that the abnormal aortic valve morphology and motion characteristics in our subgroup of patients with mitral valve prolapse, when compared to controls, is an acceptable definition for this entity. Further support is provided by the increased prevalence of aortic root dilatation and clinical aortic insufficiency in this subgroup of patients.

Six of our 17 patients with aortic valve prolapse had aortic cusp eccentricity probably due to myxomatous degeneration affecting one cusp more severely. These patients must be differentiated form those with congenital bicuspid aortic valve disease. In bicuspid aortic valve disease one cusp is usually larger and has been called the conjoined cusp.[3] The conjoined cusp may prolapse on the basis of excessive tissue relative to the distance between the two commissural attachments. The differentiation between aortic valve prolapse on the basis of the "floppy valve syndrome" or bicuspid aortic valve disease[3] may be possible using the short axis view of cross sectional echocardiography. Using this view, the presence of three separate aortic cusps would tend to exclude the presence of a bicuspid valve and, in fact, all six of our patients with an eccentric aortic cusp had three aortic valve cusps using this approach. This unfortunately does not entirely prove the absence of a bicuspid aortic valve since an uncommon form of congenital bicuspid aortic valve exists in which the center of the free edge of the conjoined cusp is joined to the aortic wall by a thin strand. This might give the impression of a tricuspid aortic valve.[3] However, since our patients were drawn from a population of patients with mitral (and often tricuspid) valve prolapse and since all six did have an apparent tricuspid valve on the short axis view, and one patient had a tricuspid aortic valve on angiography, we believe the majority, if not all of these cases did in fact have aortic valve prolapse on the basis of the "floppy valve syndrome."

In addition, this study suggests that not only congenital bicuspid aortic valves may cause eccentricity of the aortic valve closure line in diastole on M mode echocardiography,[18] but that aortic valve prolapse caused by the "floppy valve syndrome" should be considered. Though not statistically significant, the increased prevalence of tricuspid valve prolapse in patients with aortic valve prolapse suggests that a more widespread involvement of the myxomatous degenerative

Mitral valve prolapse in anxiety neurosis (panic disorder)

Alagiriswami Venkatesh, M D
David L Pauls Ph.D
Raymond Crowe M D
Russell Noyes Jr M D
Charles Van Valkenburg M D
James B Martins M D
Richard E Kerber M D
Iowa City Iowa

The typical symptoms of anxiety neurosis or panic disorder—palpitation dyspnea chest pain and dizziness—suggest a cardiovascular disturbance and in the past led to such labels as irritable heart ' effort syndrome and neurocirculatory asthenia [1] Similar symptoms may be reported by patients with the recently described syndrome of mitral valve prolapse In fact panic disorder and mitral valve prolapse share a number of clinical features Both are common disorders probably affecting 5% to 10% of the population both are frequent in young women and both may be familial [1] The characteristic physical findings of mitral prolapse a mid systolic click and late systolic murmur have not been associated with panic disorder in the past but these sounds were in general not felt to be of clinical significance until Barlow and co workers[3] demonstrated their relationship to the prolapsing mitral valve

The [illegible] ities between panic disorder and pr[illegible] [illegible]ed Wooley[4] to suggest that many pat[illegible] [illegible]d as having panic disorder might be [illegible] mitral valve prolapse Pariser and associates[5] described several such cases The purpose of this study was to test Wooley's hypothesis in a group of rigorously diagnosed patients with panic disorder

Methods

From 112 anxiety neurosis patients followed by Noyes and Clancy [6] we selected 20 patients for this study on the basis of (1) meeting Feighner and colleagues'[7] research criteria for anxiety neurosis (panic disorder) and (2) for convenience living within 100 miles of Iowa City Feighner and colleagues'[7] criteria for the diagnosis of anxiety neurosis (panic disorder) are (1) age of onset prior to 40 (2) chronic nervousness with recurrent anxiety attacks (manifested by apprehension fearfulness or sense of impending doom) occurring at times other than during marked physical exertion or life-threatening situations and in the absence of medical illness or other psychiatric illness There must have been at least six anxiety attacks each separated by at least a week from the others and (3) at least four of the following symptoms (a) dyspnea or a choking or smothering sensation (b) palpitations (c) chest pain or discomfort (d) dizziness (e) paresthesia All 20 patients who met these criteria and lived within 100 miles of Iowa City were contacted and all 20 agreed to participate One family was doubly ascertained through a mother and daughter both with panic disorder leading to a total of 21 index subjects These 15 women and six men ranged in age from 21 to 62 years with a median of 37 An

From T[illegible] [illegible]l Medicine and The Department of Psychiatr[illegible] [illegible] Hospitals and Clinics, Iowa City Iowa.

Supported [illegible] Heart Lung and Blood Institute Grant No. HL-014[illegible] [illegible] Institute of Mental Health Grant No MH 14[illegible]

Received for p[illegible] [illegible] 1980

Accepted for p[illegible] [illegible]5 1980

Reprint reques[illegible] [illegible]rber M D Dept of Internal Medicine University [illegible] Iowa City Iowa 224[illegible]

0002-8703/80/090302 + 04$00 40/0 © 1980 The C V Mosby Co

Prolapse of semilunar cusps as causes of aortic insufficiency Circulation 53 922 1971
4 Kerber R F Isaeff D M and Handcock E W Echocardiographic pattern in patients with the syndrome of systolic click and late systolic murmur N Engl J Med 283 691 1971
5 Dillon J C Haine C L Chang S and Feigenbaum H Use of echocardiography in patients with prolapsed mitral valve Circulation 43 503 1971
6 DeMaria A N King J F Bogren H C Lies J F and Mason D T The variable spectrum of echocardiographic manifestations of mitral valve prolapse syndrome Circulation 50 33 1974
7 Popp R L Brown O R Silverman J F and Harrison D C Echocardiographic abnormalities in mitral valve prolapse syndorme Circulation 49 428 1974
8 Chandraratna P A N Lopez J M Fernandez J J and Cohen L S Echocardiographic detection of tricuspid valve prolapse Circulation 51 8 3 1975
9 Werner J A Schiller N B and Prasquier R Occurrence and significance of echocardiographically demonstrated tricuspid valve prolapse Am HEART J 96 180 1978
10 Chandraratna P A N Samet P Robinson M J and Byrd C Echocardiography of the "floppy aortic valve Circulation 52 959 19 5
11 Rippe J M Angoff G Sloss L J Wynne J and Alpert J S Multiple floppy valves an echocardiographic syndrome Am J Med 66 817 1979
12 Kisslo J vonRamm O T and Thurstone F L Cardiac imaging using a phased array ultrasound system Circulation 53 II 262 1976
13 Gilbert B W Schatz R A VonRamm O T Behar V S and Kisslo J A Mitral valve prolapse Two dimensional echocardiographic and angiographic correlation Circulation 54 716 19 6
14 Feigenbaum H Echocardiography 2nd ed Philadelphia 1976 Lea & Febiger Publishers
15 Mardelli T J Morganroth J Meixell L and Vergel J Enhanced diagnosis of tricuspid valve prolapse by cross sectional echocardiography Am J Cardiol 43 385 1979
16 El Shahawy M Graybeal R Pepine C J and Conti C R Diagnosis of aortic valve prolapse by echocardiography Chest 69 411 1976
17 McKay R, and Yacoub M H Clinical and pathological findings in patients with floppy valves treated surgically Circulation 47 III 63 1973
18 Nanda N C Gramiak R Manning J, Mahoney E B Lipchik E O and DeWeese J A Echocardiographic recognition of the congenital bicuspid aortic valve Circulation 49 870 1974

Table I

	AN (N = 21)	Control (N = 20)	p
Comparison of anxiety neurosis vs control subjects			
(a) Systolic click and/or murmur	10	6	NS
(b) ECG resting ST T abnormalities	7	0	<0 01
(c) ECG PVC s during exercise	9	1	<0 01
(d) Echocardiographic prolapse	8	2	<0 05
(e) Echo prolapse plus (a)	5	1	NS
(f) Echo prolapse plus (a) or (b)	7	1	<0 05
Echocardiographic diameters†			
(g) Left ventricular end diastolic diameter (cm)	4 4 ± 0 6	4 9 ± 0 8	NS
(h) Left ventricular end systolic diameter (cm)	2 9 ± 0 4	3 1 ± 0 8	NS
(i) ΔD	0 36 ± 0 07	0 38 ± 0 08	NS
(j) Left atrial diameter (cm)	2 9 ± 0 4	3 1 ± 0 6	NS

P values are Fisher exact one tailed
†Values ± 1 standard deviation
ΔD = fraction of minor axis shortening

prolapse plus click murmur and/or exercise induced PVC s Within the panic disorder group patients with mitral valve prolapse determined by echocardiogram and those without prolapse had a similar incidence of clicks and/or murmurs and electrocardiographic abnormalities

Discussion

In this study eight of 21 panic disorder patients had echocardiographic evidence of mitral prolapse Seven of these had auscultatory or electrocardiographic findings suggestive of the mitral prolapse syndrome in addition to echocardiographic demonstration of prolapse Of the two control subjects with echocardiographic evidence of prolapse only one showed additional abnormalities on auscultation or electrocardiogram Thus mitral prolapse was identified significantly more often among the panic disorder patients than among the controls ($p < 0.05$) This finding suggests that a substantial number of patients bearing the psychiatric diagnosis of panic disorder also have an organic abnormality mitral valve prolapse

The panic disorder patients in this study were selected solely on the basis of meeting diagnostic criteria for panic disorder and also by geographic proximity to the medical center However they were part of a larger group which had originally been selected from patients referred to the University of Iowa Clinics This raises the question of whether the larger group contained patients with abnormal cardiac findings who might have been preferentially referred for evaluation The possibility of such a selection bias was assessed by reviewing the original patient records This revealed that most had been referred to the Internal Medicine and Neurology Clinics for evaluation of symptoms which their referring physician thought might have been associated with physical disease Heart murmurs were noted at the time of the original evaluation in only four patients and none were considered at that time to have symptoms of cardiac origin

Although we were able to demonstrate prolapse in many of these panic disorder patients the simultaneous occurrence of these conditions does not necessarily imply a causal relationship Why patients with mitral prolapse develop symptoms such as chest pain dyspnea and palpitations cannot at this time be answered It is conceivable that both panic disorder and mitral prolapse are manifestations of some underlying disorder as yet undefined

Although this study is a preliminary one the results support the link between anxiety neurosis or panic disorder and the mitral valve prolapse syndrome as proposed by Wooley[4] Patients with symptoms of panic attacks should be suspected of having the mitral prolapse syndrome Echocardiography electrocardiography and stress testing are diagnostically useful in such patients

Summary

Our purpose was to determine the incidence of mitral valve prolapse in patients with anxiety neurosis or panic disorder with symptoms including recurrent anxiety attacks dyspnea palpitations chest pain dizziness and paresthesias Twenty one patients and 20 age and sex matched normal controls were studied Objective cardiac abnormalities were significantly ($p < 0.05$) more frequent in the patient group as compared to the control group these comprised echocardiographic prolapse ST T abnormalities

age and sex matched control group was selected from hospital employees There were 14 women and six men with a median age of 37 (range 23 to 62 years) This group was specifically free of anxiety symptoms and denied a history of heart disease

The study was approved by the Human Research Committee of the University of Iowa informed written consent was obtained from all participants

A medical history was obtained from all subjects with specific questioning for symptoms of panic disorder A physical examination was performed by a cardiology fellow During the cardiovascular examination systolic clicks and murmurs were sought by auscultation in the supine and upright positions Resting and exercise electrocardiograms were obtained using the Bruce exercise protocol Echocardiograms were performed on all patients using a Smith Kline Ekoline 20A ultrasonoscope with a 2 5 mHz transducer focused at 7 5 cm and a Honeywell 1856 fiberoptic strip chart recorder The mitral valve recordings were obtained by positioning the transducer perpendicular to the chest wall as recommended by Popp and co workers

The echocardiographic criteria for mitral prolapse were those of Markiewicz and colleagues[1] The points of coaptation (C point) and separation (D point) were identified and a line was drawn between the two (C D line) Echocardiographic prolapse was considered to be present if the predominant systolic mitral echo extended more than 2 mm posteriorly from the C D line either in a smooth concave hammock shaped fashion (holosystolic prolapse) or as a sharp mid late systolic buckling The echocardiograms were read by an observer who was not otherwise involved in the study and who did not know if the recording was from an index subject or a control

Left ventricular diameters were measured at end diastole (R wave of ECG) and end systole (smallest distance between posterior wall and septum) Left atrial diameters were measured at end systole

Results

The results are summarized in Table I Ten panic disorder patients had systolic clicks and/or murmurs on auscultation Of these murmurs two were holosystolic five were mid late systolic one was early systolic and one was variable between examinations Two patients had mid late systolic clicks (one of these also had a murmur) No patient had skeletal abnormalities associated with mitral valve prolapse such as pectus excavatum

Seven patients showed ST T wave abnormalities on resting electrocardiograms two of these seven patients were taking tricyclic antidepressant drugs which may have caused or contributed to these electrocardiographic findings No patient developed angina or ST T changes with exercise all but one achieved 85% of the age predicted maximum heart rate One patient had premature ventricular contractions (PVC s) at rest nine had PVC s with exercise (one had PVC s occurring in couplets during exercise)

Systolic prolapse was demonstrated by echocardiogram in eight panic disorder patients four holosystolic and four mid late systolic Of the eight panic disorder patients with echocardiographic evidence of prolapse five had clicks and/or murmurs and two others had PVC s on exercise Only one patient with echocardiographic evidence of prolapse had no additional abnormality

Six control subjects had systolic clicks and/or murmurs (Table I) On auscultation two had holosystolic murmurs and one had a mid late systolic murmur Four patients had mid late systolic click (one of these also had a murmur) One control subject had PVC s at rest and another developed them with exercise Three control subjects developed ST T changes with exercise but none experienced angina Two had echocardiographic evidence of prolapse one holosystolic and one mid late systolic Of these two control subjects with evidence of prolapse one had a systolic click and resting PVC s while the other had no additional abnormality

Echocardiographically determined left ventricular and left atrial volumes and left ventricular minor axis shortening (ΔD) were normal for both groups There were no significant differences between the groups in these measurements.

Differences between groups were assessed for significance using Fisher s exact test or in the case of echocardiographic diameters a Student s t test was used (Table I) Patients with panic disorder had a significantly higher incidence of echocardiographically demonstrated prolapse resting electrocardiographic ST T abnormalities exercise induced PVC s and echocardiographic

Evaluatıon of left atrıal thrombus wıth computed tomography

Haruo Tomoda M D *
Mıtsumoto Hoshıaı M D
Ryusuke Tagawa M D
Shırosaku Koıde M D **
Shıakı Kawada, M D
Akıra Shotsu M D
Seıya Matsuyama, M D ***
Kanagaua Japan

Detectıon of ıntra atrıal thrombı ın patıents wıth mıtral valvular dıseases ıs very ımportant ın determınıng the applıcatıon of antıcoagulant therapy or surgıcal treatment Angıographıc and echocardıographıc evaluatıons of left atrıal thrombı have been reported [1 3] but small thrombı located ın the left atrıal appendage have been assocıated wıth dıffıcultıes ın detectıon by con ventıonal methods [1 2] On the other hand prelım ınary reports on the possıble applıcatıon of com puted tomography ın the fıeld of cardıology have recently become avaılable [4 6] Harada and asso cıates[7] have demonstrated the possıbılıty of detectıng left atrıal thrombus wıth computed tomography The present study was ıntended to show the usefulness of computed tomography ın the evaluatıon of left atrıal thrombı

Materıals and methods

Twenty three patıents wıth mıtal valvular dıs eases were studıed (nıne wıth mıtral stenosıs three wıth mıtral regurgıtatıon and 11 wıth mıtral stenosıs regurgıtatıon) Thırteen of these cases subsequently underwent cardıac surge and two of them had autopsy A comput tomographıc whole body scanner whıch utılıze contınuously rotatıng gantry and pulsed anc wıth x ray radıatıon collımated to form a tl fan shaped beam was used [a*] A complete sectı scan was performed ın 3 seconds The scale x ray transparency (CT number) was −1 000 for aır 0 for water and +1 000 for bone To protect the qualıty of the tomograms gated computed tomographıc scannıng to obtaın stop actıon ımages[8] was not applıed ın the present study All computed tomograms were obtaıned ın the pos tıon of deep ınspıratıon Sustaıned enhancement was obtaıned wıth a rapıd ıntravenous ınfusıon of 30% meglumıne ıothalamate (200 to 300 ml)

Results

Left atrıal thrombı were revealed ın the follow ıng three cases and were compared wıth the surgıcal or postmortem fındıngs

Patıent 1 A 45 year old woman presented wıth auscultatory fındıngs compatıble wıth mıtral ste nosıs regurgıtatıon and trıcuspıd regurgıtatıon She had at least two well documented hıstorıes of bılateral heart faılure and had been placed on dıgıtalıs and furosemıde for the past 5 years She dıd not have any epısode suggestıve of systemıc embolızatıon Electrocardıograms showed rıght ventrıcular hypertrophy and atrıal fıbrıllatıon Echocardıographıc (UCG and two dımen ıonal)

From the Departme t of Card ology Surgery and Rad ology School of Med cıne Toka U rs ty Kanag wa, Japan
Recei ed f r p bl t n Feb 4 1980
Accepted fo p bl at on Feb 2 1980
Reprınt requests H ruo Tomoda M D D pt of C rdıol gy (Naıka) School of Medıcıne Tok Un rsıty Boseıdaı, Isehara shı, Kanaga wa ken Japan 259-11
*Dept of C rd ol gy School of Med cıne Tok ı Unıvers ty
**Dept of Surgery School of Med e Tokaı Unıversıty
***Dept of Radıology School of Med cı Tokaı Unıversıty

a Varıan Computed Tomograph c Whol Body Sc n r

0002 8703/80/090306 + 05$00 50/0 © 1980 The C V Mosby Co

on resting ECG premature ventricular contractions on exercise ECG and the combination of echo prolapse with clicks/murmurs or exercise induced PVC We conclude that patients with anxiety neurosis or panic disorder may also have evidence of an organic abnormality—the mitral prolapse syndrome

REFERENCES

1 Cohen M E and White P D Life situations, emotions and neurocirculatory asthenia (anxiety neuro is neurasthenia effort syndrome) Assoc Res Nerv Ment Dis Proc 29 832 1950
2 Devereux R B Perloff J K Reichek N and Josephson M E Mitral valve prolapse Circulation 54 3 1976
3 Barlow J B Pocock W A Marchand P and Denny M The significance of late systolic murmurs AM HEART J 66 443 1963
4 Wooley C F Where are the diseases of yesteryear? DaCosta s syndrome oldiers heart the effort syndrome neurocirculatory asthenia—and the mitral valve prolapse syndrome Circulation 53 749 1976
5 Pariser S F Jones B A Pinta E R Young E A, and Fontana M E Panic attacks Diagnostic evaluations of 17 patients Am J Psychiatry 136 105 1979
6 Noyes R and Clancy J Anxiety neurosis a five year follow up J Nerv Ment Dis 162 200 1976
7 Feighner J P, Robins E Guze S B Woodruff R A Winokur G and Munoz R Diagnostic criteria for use in psychiatric research Arch Gen Psychiatry 26 57 1972
8 Bruce R A and Hornsten T R Exercise stress testing in evaluation of patients with ischemic heart disease Progr Cardiovasc Dis 11 371 1969
9 Popp R L Filly K Brown D R and Harrison D L Effect of transducer placement on echocardiographic measurement of left ventricular dimension Am J Cardiol 35 537 1975
10 Markiewicz W Stoner J London E, Hunt S A, and Popp R L Mitral valve prolapse in 100 presumably healthy young females Circulation 53 464 1976

IMPORTANT
INFORMATION FOR AUTHORS

All manuscripts for the AMERICAN HEART JOURNAL should be sent to

Dean T Mason M D
Section of Cardiovascular Medicine
University of California
School of Medicine
Davis California 95616

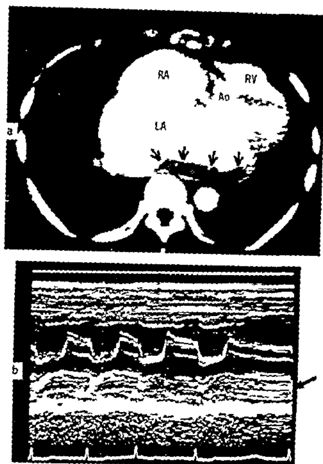


Fig 3 A patient with mitral stenosis-regurgitation atrial fibrillation and two histories of cerebral thromboses (Case No 3) *A* computed tomogram at the level of the left atrium a thrombus (7 5 cm × 1 7 cm × 3 cm) is indicated by *arrows* *RA* = right atrium *RV* = right ventricle *Ao* = aorta *LA* = left atrium *B* echocardiographic findings in the same patient (the thrombus is indicated by an *arrow*)

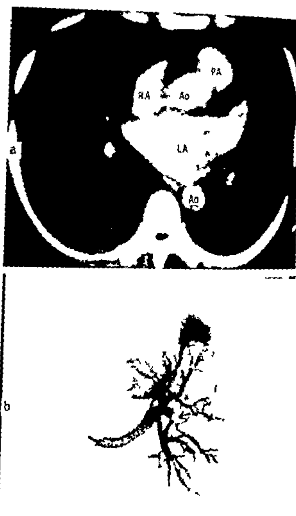


Fig 4 A patient with mitral stenosis regurgitation at fibrillation and a history of renal thrombosis There i thrombus lodged in the dorsal branch of the left renal art as indicated by an *arrow* *(B)* but there is no left at thrombus demonstrated with computed tomography *(A)* C diac surgery subsequently performed also revealed no l atrial thrombus *RA* = right atrium *Ao* = aor *PA* = pulmonary artery *LA* = left atrium

Hg pulmonary capillary wedge—15 mm Hg (mean) and aorta—106/64 mm Hg

The left ventricle was not entered via the retrograde route due to severe aortic stenosis Cineangiographic findings (levophase pulmonary arteriography and aortography) revealed mitral stenosis aortic stenosis with regurgitation and enlarged left atrium There was an insufficient filling of the left atrial appendage which suggested a thrombus in the area of the left atrial appendage

Computed tomograms at the left atrial level revealed two spherical thrombi—one located at the atrial appendage with a tomographically measured size of 2 0 cm × 2 3 cm and another located at the right posterior wall of the left atrium with a measured size of 2 0 cm × 2 9 cm (Fig 2) She was operated on for valve replacement and a total of 20 gm of left atrial thromb which were consistent with the shapes and sizes detected by computed tomographic method was excised

Patient 3 A 68 year old woman presented with mitral stenosis regurgitation atrial fibrillation and with two previous episodes of cerebral thromboses and another episode of bilateral femoral arterial thrombosis Right heart catheterization was performed and intracardiac pressures were as follows right atrium—5 mm Hg (mean) right ventricle—40/5 mm Hg pulmonary artery—50/20 (mean 30) mm Hg and pulmonary capillary wedge—26 mm Hg (mean) A levophase pulmo-

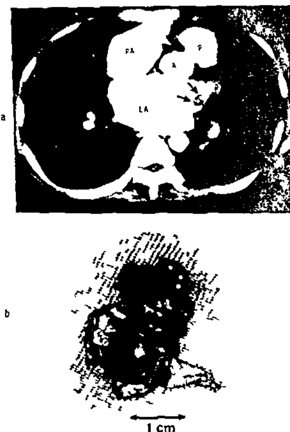


Fig 1 A patient with mitral stenosis regurgitation tricuspid regurgitation, and atrial fibrillation (Case No 1) *A* computed tomogram at the level of the left atrium a thrombus (1 3 cm × 1 6 cm) is indicated by *arrows* *RA* = right atrium *RV* = right ventricle *Ao* = aorta *LA* = left atrium *B* surgically excised thrombus of the same patient (3 5 gm)



Fig 2 A patient with mitral stenosis regurgitation aortic stenosis regurgitation atrial fibrillation and a history of cerebral thrombosis (Case No 2) *A* computed tomogram at the level of the left atrium a thrombus (? 0 cm × 2 3 cm) is shown by an *arrow* at the atrial appendage *B* another thrombus (? 0 cm × 2 9 cm) is indicated by an *arrow* at the right posterior wall of the left atrium which is ? cm lower than the appendage level *SVC* = superior vena cava *Ao* = aorta *PA* = pulmonary artery *LA* = left atrium

findings of the patient were compatible with mitral stenosis minimal regurgitation and tricuspid regurgitation but no left atrial thrombus was detected echocardiographically

Intracardiac pressures were as follows right atrium–6 mm Hg (mean) right ventricle–90/7 mm Hg pulmonary artery–97/37 (mean 58) mm Hg pulmonary capillary wedge–24 mm Hg (mean) left ventricle–124/13 mm Hg and aorta–129/79 mm Hg Cineangiographic findings (levophase of pulmonary angiogram and left ventriculogram) revealed thickened and stenosed mitral valves grade 1 mitral regurgitation, and a markedly enlarged left atrium but no thrombus was detected cineangiographically

On the other hand computed tomography at the level of the left atrium indicated a filling defect in the left atrial appendage measured as 1 3 cm × 1 6 cm on the tomogram (Fig 1*a*) Open mitral commissurotomy was performed 4 days after the computed tomographic evaluation and a well-organized thrombus of 1 cm × 1 5 cm × 2 cm (weight 3 5 gm) was found in the left atrial appendage and was excised (Fig 1*b*)

Patient 2 A 47 year old woman presented with mitral stenosis regurgitation aortic stenosis regurgitation and atrial fibrillation She had a history of cerebral thrombosis a year ago with persistent right hemiplegia Phonocardiographic and echocardiographic findings were compatible with the above diagnoses and the presence of left atrial thrombi was suspected echocardiographically Intracardiac pressures were as follows right atrium–4 mm Hg (mean) right ventricle–34/3 mm Hg pulmonary artery–35/16 (mean 23) mm

results with computed tomography in 13 patients who subsequently underwent cardiac surgery Computed tomography is essentially noninvasive and appears to be one of the best methods to evaluate left atrial thrombus

REFERENCES

1 Parker B M Friedenberg M J Templeton A W and Burford T H Preoperative diagnosis of left atrial thrombi in mitral stenosis N Engl J Med **273** 136 1965

2 Spangler R D and Okin J T Echocardiographic demonstration of a left atrial thrombus Chest **67** 716 1975

3 Mikell F L Asinger R W Rourke T Hodges M Sharma B and Francis G S Two dimensional echo cardiographic demonstration of left atrial thrombi in patients with prosthetic mitral valves, Circulation **60** 1183 1979

4 Ter Pogossian M M Weiss E S and Bokel, B E. Computed tomography of the heart Am J Roentgenol **127** 79 1976

5 Huang H K and Mazziotta J C Heart imaging from computerized tomography Comput Tomography 2 3 1978

6 Guthaner D F Wexler L and Harell G CT demonstration of cardiac structures Am J Roentgenol **133** 75 1979

7 Harada J., Kobayashi, H and Tada S Computed tomography in cardiac diseases with special emphasis on mitral valve disease (in Japanese) J Cardiography 9 417 1979

8 Harell, G S Guthaner D F Breiman, R S Morehouse C C Seppi E J Marshall W H and Wexler L Stop action cardiac computed tomography Radiology *123* 515 1977

nary arteriogram revealed an enlarged left atrium with a thrombus located at the posterior wall of the left atrium

Computed tomographic findings demonstrated a large left atrial thrombus measuring 7 5 cm × 1 7 cm (the height was estimated as an average of 3 cm) located at the posterior wall of the left atrium (Fig 3a) The thrombus attached to the posterior wall of the left atrium was easily demonstrated echocardiographically as shown in Fig 3b The computed tomographic findings were confirmed by autopsy performed 3 months after the tomographic evaluation and the weight of the thrombus was approximately 40 gm

Discussion

Detection of left atrial thrombi in patients with mitral valvular diseases is of significant importance regardless of the size of the thrombi because the patients are always faced with the possibility of systemic embolization Parker and colleagues have demonstrated that atrial thrombi were predicted correctly angiographically in six out of 70 patients who subsequently had cardiac surgery but thrombi could not be detected in two patients Echocardiography is noninvasive and one of the most hopeful methods for detecting atrial thrombi in patients with mitral valvular diseases

Recently Mikell and associates demonstrated atrial thrombi correctly by two dimensional echocardiography and the minimum thrombus detected echocardiographically as a spherical aggregate approximately 1 5 cm in diameter

On the other hand due to the limitation in the direction of echo beam projection small thrombi located in the left atrial appendage or in the right edge of the left atrium are difficult to detect echocardiographically[2] Computed tomography has the advantage of offering uniform slices of the left atrium in an attempt to detect thrombi in unknown areas of the left atrium The method is not disturbed by the presence of the ribs or thoracic cage as in the case of echocardiography

Both fresh and organized thrombi were delineated with computed tomography and the nature of the thrombi might be possible to estimate by the difference in the x ray transparency i e the CT numbers In Case No 1 the thrombus was mostly organized with partial fibrosis and the CT number was +68 In Case 2 the thrombi were almost fresh without fibrosis and the CT number was +42 which was identical to that of the left ventricular chamber (+40) The CT number was not recorded in Case 3

The minimum size of the thrombi detected tomographically was 3 5 gm as shown in Case 1 but the lowest limit of the thrombus size which can be detected is still not known although there is the possibility that an extremely small thrombus might be missed by any method In another 51 year old woman with mitral stenosis regurgitation and atrial fibrillation an episode of renal thrombosis was encountered 6 days before the tomographic evaluation and a thrombus 0 2 cm × 0 4 cm in size and lodged in the dorsal branch of the left renal artery was demonstrated angiographically

However there was no left atrial thrombus apparent in computed tomography and cardiac surgery performed subsequently did not reveal a left atrial thrombus which appeared to have been washed out completely (Fig 4) Therefore there have been no false negative or false positive cases experienced so far

The stop action method gated with ECG is possible in the system used in the present study[7] but our impression is that the quality of the tomogram is not satisfactory due to reduced data sampling numbers for every frame of the tomogram Therefore it should be noted that the configurations of the various cardiac structures obtained by computed tomography are affected by the effects of cardiac movements Fortunately however the cardiac movements are relatively limited at the cardiac base especially in enlarged atria with fibrillation

Computed tomography is a noninvasive method and based on our experience in a limited number of patients it appears to be one of the best methods in evaluating left atrial thrombi to determine the details necessary for medical or surgical treatment

Summary

Left atrial thrombi were evaluated with computed tomography in 23 patients with mitral valvular diseases In three of the patients left atrial thrombi were delineated with computed tomography and were confirmed by cardiac surgery or autopsy The minimum size of the thrombi detected tomographically was 3 5 gm

There were no false positive or false negative

Table I Analysis of survivors, nonsurvivors and mortality rates according to age by decade of life and by sex

Age group	No of survivors		No of non survivors		% mortality		σ total mortality
	Male	Female	Male	Female	Male	Female	
Group B							
30-39	29	4	0	0	0	0	0
40 49	90	24	6	1	6 3	4 0	5.8
50 59	212	57	17	6	7 4	9 5	7 8
60 69	192	101	21	12	9 9	10 6	10 1
Total	523	186	44	19	7 8	9 3	8.2
Group A							
70 79	50	38	18	23	26 5	37 7	31 8
80 89	10	20	4	10	28 6	33 3	31.8
90 99	0	1	1	0	100	0	50 0
Total	60	59	23	33	27 7	35 9	3?0

Table II Prevalence of various prognostic factors and the mortality risk of each prognostic factor in survivors and nonsurvivors

Prognostic factor	% prevalence in study group (Group A)	No of survivors	No of non survivors	% mortality	p value
History of angina pectoris	54 3	64	31	32 6	0 84
Hypertension	44 0	53	24	31 2	0 91
History of prior MI	33 1	39	19	3? 8	0 8?
History of CHF	20 0	23	12	34 3	0 7
Diabetes mellitus	21 7	23	15	39 5	0 ?4
Total		119	56		

Abreviations MI = myocardial infarction CHF = congestive heart failure

of life for all patients admitted during the study period The over all mortality rate for the elderly group was 32% There was no difference between the mortality rate for the 70 to 79 year age group (31 8% mortality) and the 80 to 89 year age group (31 8% mortality) The mortality rate for all elderly females studied was 35 9% as compared to 27 7% for all elderly males (Table I) This was not statistically significant (p = 0 25 by Chi square analysis) There werre 772 patients below age 70 admitted during the same time frame that were analyzed for mortality related to age and sex (Group B) Table I shows that the over all mortality rate was 0 below age 40 and increased progressively for each decade of life This was true for both men and women Women had a slightly higher mortality rate for each decade after age 49 The total mortality rate for men under age 70 was 7 8% for women it was 9 3% and for the total group it was 8 2%

The following prognostic factors were studied in the elderly group to determine their association with prognosis a history of angina pectoris myocardial infarction (MI) hypertension congestive heart failure (CHF) or diabetes mellitus The prevalence of each of the above potential prognostic factors in the group was history of angina pectoris 54 3% history of MI 33 1% history of hypertension 44 0% history of CHF 20 0% and history of diabetes mellitus 21 7% (Table II) No single prognostic factor was associated with a significant increase in mortality rate during the hospital course

The mortality rate of patients with no prognostic factors was 24 3% with one prognostic factor it was 41% with two prognostic factors it was 25 5% with three prognostic factors it was 42 4% and with four prognostic factors it was 25% (Table III) There was no associated increase in mortality rate with an increase in the number of prognos

ıcute myocardial infarction in hospitalized ıatients over age 70

:lifton A Latting M D *
ıark E Silverman M D **
tlanta Ga

ılthough the clinical course and prognosis of ıatients with acute myocardial infarction has ıeen carefully studied little attention has been ıiven to the effect of age on mortality rate

In this paper we present the age sex and ıospital mortality rate and analyze the factors nfluencing prognosis in a group of patients aged '0 years and older with acute myocardial infarc ion A comparison is made with the mortality ate of all patients less than 70 years of age who ıere admitted during the same time period

ʾatients and methods

The elderly study group (Group A) included all ıatients admitted to the coronary care unit of ʾiedmont Hospital between May 1 1971 and Ianuary 31 1977 who met the following crite ıa

1 age 70 years or greater

2 a diagnosis of acute myocardial infarction (MI) on the *basis of any two of the following* three factors—

a prolonged chest discomfort compatible with myocardial injury

b characteristic electrocardiographic changes of myocardial infarction including serial ST T changes or the development of pathologic Q waves

c elevation of serum creatine phosphoki nase (CK) to at least two times the upper limits of the normal range

A total of 175 patients met two or more of these criteria All patients were observed in the coro nary care unit with continuous monitoring No drugs were given routinely without specific indi cations Data were obtained in a retrospective manner from a comprehensive data base acquired at the time of admission on all patients to the coronary care unit as well as from a review of physician s office records prior to admission A prior history of angina pectoris myocardial infarction diabetes mellitus hypertension (sys tolic BP equal to or greater than 160/90 mm Hg) and congestive heart failure was noted The phy sician s office records did not always contain the physician s specific diagnostic criteria therefore this information was considered as historical information and consequently does not meet rigid standards of definition Serial electrocardiograms (ECG s) were evaluated to determine the electro cardiographic site of the myocardial infarction and the presence or absence of a conduction defect Shock was defined as a systolic blood pressure of 90 mm Hg or less associated with a urine output of less than 20 c c /hr Complica tions occurring during the AMI were determined from a review of the hospital record the detailed data base compiled during the admission and a review of all ECG s and chest films reports The cause of death was determined from the hospital record or autopsy reports

Group B was composed of 772 patients below age 70 with acute MI who were admitted to the hospital during the same time period The age and sex related hospital mortality rate of this younger age group was compared with the study group

Results

There were 175 patients in Group A—83 (47 4%) were male and 92 (52 6%) were female Table I shows the age sex and mortality rate per decade

From the Departm nt of Med cin Fm ry U vers ty School of Medi e nd Piedm t Hosp tal, Atla ta Ga.

Rec ed f r Publi tion Feb 4 1980

Acc pted f r publi tion Apr 24 1980

* F ll w in C rd l gy Em ry Uni rs ty Schoo l of Medi ine

** Professo of Medi ine (Card ol gy) Fmory U v rs ty School f Medicin

0002 8 03/80/090311 + 08$00 80/0 © 1980 The C V Mosby Co

of the deaths due to anterior MI The major cause of death in the 16 patients with inferior MI was shock in four patients (25%) and sudden death in three (18 8%) accounting for 43 8% (seven of 16) of the 16 deaths due to inferior MI

The ten patients with autopsy documented external cardiac rupture had several distinguishing characteristics The sex was predominantly female (seven of 10) Nine of the ten patients had no history of prior MI The cardiac rupture generally occurred during the first 48 hours of hospitalization (seven of 10) and was within 60 hours of the onset of symptoms in the seven cases There were seven ruptures of the anterior wall two of the inferior wall and one rupture of the apex This distribution paralleled the distribution of the myocardial infarctions in the entire study group (anterior MI 66 9% inferior MI 33 1% Table IV) The location of the external myocardial rupture was always in the site of the acute myocardial infarction as determined by ECG and as noted at autopsy

There were nine patients who died suddenly without autopsy Four of these nine patients sustained a final clinical event that was marked by sudden cardiorespiratory arrest with a bradycardia observed on the ECC monitor and with absent pulses on physical examination Myocardial rupture was suspected in these four patients The remaining five patients who died suddenly were not monitored at the time of death and the cause of the final event was not apparent

Discussion

Patients with myocardial infarction in the age group 70 and older differ in their sex distribution clinical course and hospital mortality rate when compared to patients younger than age 70 In this study of 175 patients aged 70 and older the male female ratio was 0 9 1 0 (Table I) In contrast the male female ratio of our 772 patients under age 70 admitted during the same time period was 2 77 1 0 while under age 60 the male female ratio was 3 85 1 0 In reported series of patients less than 70 years of age there is a striking male preponderance Fitzgerald[2] studied 865 patients with acute MI and found the male female ratio to be 7 1 below age 50 10 1 between age 50 and 59 and 4 1 in the age group 60 to 69 Following a peak in the sixth decade male preponderance declines rapidly until the eighth decade when the male female ratio approaches 1 1 in most large series[1]

The prevalence of certain prognostic factors in the age group 70 years and older is higher than the incidence of similar factors reported in younger age groups Frank[5] studied 881 men aged 25 to 64 who had their first MI The incidence of angina pectoris was 17% hypertension was 25% congestive heart failure was 4% and diabetes mellitus was 11%[5] In our elderly group of patients the incidence of angina pectoris was three times hypertension was 1 8 times congestive heart failure was five times and diabetes mellitus was two times the incidence in the study by Frank (Table IV) A history of prior MI was present in 33 3% of our patients This is similar to the 28% to 38% prevalence of prior MI reported in several studies of younger patients[6-10]

The increased prevalence of these prognostic factors in our elderly group was not however associated with an increased mortality rate (Table II) There were no prognostic factors present in 23 5% of the survivors or in 16 1% of the nonsurvivors (Table III) The mortality rate of patients with zero one two three and four prognostic factors represented a random distribution (Table III) Hospital mortality rate was not influenced by the number of prognostic factors present in individual patients (Table III) nor by the over all prevalence of prognostic factors in the entire study group (Table II)

Factors that significantly influenced hospital mortality rate from acute MI were the development of shock pulmonary edema on chest x ray a clinical diagnosis of congestive heart failure and the development of complete heart block or new bundle branch block during the hospital course ($p \leq 0\ 01$ Table IV) These complications are usually associated with the loss or dysfunction of a significant amount of ventricular muscle from the new or any prior MI In this study there was a significantly high mortality rate of 88 9% associated with complete heart block ($p = 0\ 001$ Table IV) Although all three of the patients with new BBB died the hospital mortality rate associated with the presence of BBB in general including BBB known to be present prior to the acute myocardial infarction was not significantly increased ($p = 0\ 26$ Table IV) This discrepancy may be due to the high incidence of pre-existing BBB on the basis of Lev s or Lenegre s disease in the elderly[11-13] Bundle branch block related to these causes may not signify the same degree of muscle necrosis or ventricular dysfunction as BBB resulting from acute myocardial infarction

tic factors per patient (p = 0.25 by Chi square analysis).

Hospital course. The serial ECGs and hospital course of the 175 elderly patients were reviewed to determine whether or not factors could be identified which were associated with increased hospital mortality rate. The mortality rate of patients with anterior MIs (32.7%) was not significantly different from that of patients with inferior MIs (30.2%, Table IV). The development of either complete heart block or a new bundle branch block on the ECG was associated with a high mortality rate (Table IV). Eight of the nine patients (88.9%) with complete heart block died despite temporary cardiac pacing. Complete heart block was associated with an anterior MI in five patients (55.6%), inferior MI in three patients (33.3%), and an undetermined site in one patient. Twenty-one patients had a bundle branch block, a right bundle branch block (RBBB) was present in ten, and a left bundle branch block (LBBB) was present in 11 (Table IV). The development of a new bundle branch block (BBB) during the hospital course was documented in only three patients (1.7%) all of whom died. There were 18 patients with BBB on the admission ECG, nine of these 18 cases could be documented as being present previously. On admission to the hospital one patient had a LBBB which subsequently resolved. The remaining eight cases of BBB were of unknown duration. The mortality rate of all patients with old or new BBB was 42.9% (nine of 21). Five of the 56 patients who died had RBBB and four had LBBB.

Cardiogenic shock, pulmonary edema on chest x-ray, CHF by examination, and complete heart block occurring on admission or during the hospital course were all associated with a significant mortality rate ($p < 0.01$, Table IV). The presence of shock either on admission or developing during the hospital course was associated with an 80% mortality rate (24 of 30). Pulmonary edema documented on chest x-ray and occurring at any point during the hospital course was associated with a 60% mortality rate (15 of 25). Congestive heart failure (CHF) as defined by rales, jugular venous distention, and/or a ventricular gallop was associated with a mortality risk of 39.6% (42 of 106).

Hospital deaths. The records of the elderly patients dying in the hospital were analyzed to determine the specific cause of death (Table V). The over all hospital mortality rate was 32% (56 of 175). The major cause of death was shock

Table III. Comparison of the number of prognostic factors in survivors and nonsurvivors

		Number of prognostic factors						
		0	1	2	3	4	5	Total
Survivors	No.	28	23	38	19	9	2	119
	%	23.5	19.3	31.9	16	7.6	1.7	
Non survivors	No.	9	16	13	14	3	1	56
	%	16.1	28.6	23.2	25	5.4	1.8	
% mortality according to the number of prognostic factors present		24.3	41	25.5	42.4	25		

accounting for 33.9% (19 of 56) of the deaths. Of the 19 patients who died of shock, 13 of 19 had anterior infarctions (68.4%), four of 19 had inferior infarctions (21.1%), and two of 19 had an undetermined site of infarction (10.5%). Mitral regurgitation was present in three of the four patients with shock related to an inferior infarction. The inferior MI was associated with a prior anteroseptal MI in the remaining patient.

External cardiac rupture was documented in 10 of 23 patients studied at autopsy (Table V). This represented 17.9% of the 56 deaths and was the second major cause of death. Sudden death (unwitnessed and unmonitored) accounted for an additional nine deaths representing 16% of the total mortality. A significant number of these deaths may have been cardiac rupture (discussed below), however autopsies were available on only two of the nine. The remainder of the deaths were due to severe CHF (six patients—10%), arrhythmia (four patients—7.1%), GI bleeding (two patients—3.6%), aspiration (one patient—1.8%), and aortic dissection (one patient—1.8%). Two patients (3.6%), one with an anterior and one with an inferior MI, developed ventricular septal rupture and both died postoperatively following surgical repair. The cause of death could not be determined from the record in two cases (3.6%, Table V).

The major cause of death in the 35 patients with anterior MI was extensive muscle damage. This was manifested by shock in 13 of the 35 cases (37.1%) and severe CHF in five of the 35 cases (14.3%) (Table V), accounting for 51.4% (18 of 35)

Table V Causes of death related to electrocardiographic site of infarction

Cause of Death		Ant MI	Inf MI	LBBB	Total no	% of deaths
Shock		13	4	2	19	33.9
Cardiac rupture		8	2		10	17.9
Sudden death	Sudden loss of consciousness associated with respiratory arrest bradycardia and absent pulses	3	0	1	4	7.1
	Sudden death of unknown cause	2	3		5	8.9
Severe CHF		5	1		6	10
Arrhythmia		3	1		4	7.1
GI bleeding			2		2	3.6
Aspiration			1		1	1.8
Aortic dissection			1		1	1.8
						1.8
Ruptured ventricular septum		1	1		2	3.6
Unknown				2	2	3.6
Total non survivors		35	16	5	56	100

MI = myocardial infarction CHF = congestive heart failure LBBB = left bundle branch block GI = gastrointestinal Ant = anterior Inf = inferior

of cardiac rupture The incidence of cardiac rupture in documented acute MI s has been reported to be 3 8% to 27%[21 25] Most series have reported an average incidence of about 10%[21 23 26] An increased incidence of cardiac rupture has been found in the elderly and in females[26-29] The majority of cardiac ruptures are reported to occur during the first 3 days following the onset of the symptoms of acute MI[22 23 30] Cardiac rupture occurred during the first 48 hours of hospitalization and within 60 hours of the onset of symptoms in 70% of our autopsy-documented cases In this study 70% of the patients with cardiac rupture had definite transmural MI s and the remaining 30% had acute MI s of undetermined extent at the time of death from cardiac rupture The association of external cardiac rupture with a first MI (nine of 10 patients in this study) is attributed to the absence of significant collateral vessels and fibrosis in the area of acute infarction where the rupture develops [2]

The hospitality mortality rate from an acute MI in the elderly group of 175 patients was 32% (Table I) This was 3 9 times greater than the mortality rate of 8 2% in our younger group The mortality rate reported in several studies in the literature for predominantly younger hospitalized patients with MI (age 70 and younger) is 8% to 20% (average 15%)[1 23 31 34] The explanation for the increased mortality rate in the elderly has not been well defined There is a higher incidence of associated prognostic factors i e previous MI shock CHF etc in elderly patients Russek and Zohman[35] divided patients above and below 60 years of age into good risk and poor risk groups Two thirds of the patients 60 years and older were shown to be poor risks compared to 47% of patients less than 60 years of age[35] There was no significant difference in mortality rate between the older and younger groups when the risk factors were comparable Russek and Zohman concluded that age itself was not an independent risk factor Our findings differ from theirs and indicate that age is a significant independent prognostic factor When the mortality rate in our good risk elderly group (patients with no prognostic factors Table III) is compared to the mortality rate of our younger patients (Group B) with and without prognostic factors the mortality rate in the good risk older age group is 2.7 times that of the entire younger age group (24.3% vs 8.9%) Age therefore is a significant independent prognostic factor even when the "good risk" older patients are compared with younger patients

The high mortality rate from an acute MI in

Table IV Mortality risk related to electrocardiographic site of infarction and various complications occurring during the hospital course

Complication	Survivors	Non-survivors	% prevalence in study group	% mortality	p value
Site of MI					
Anterior	72	35	61.1	3[illegible].7	
Inferior	37	16	30.3	30.2	
Unknown	10	5	8.6	33.3	
Shock	6	24	17.1	80	0.001
Pulmonary edema on CXR	10	15	14.3	60	0.01
CHF	64	42	60.6	39.6	0.01
Complete heart block					
Anterior	0	5			
Inferior	1	2	5.1	88.9	0.001
Unknown	0	1			
LBBB					
Admission ECG	7	3	5.7	30.0	
Developed in hospital		1	0.5	100	0.26
RBBB					
Admission ECG	5	3	4.6	37.5	
Developed in hospital		2	1.1	100	
Total	119	56			

MI = myocardial infarction CXR = chest x ray CHF = congestive heart failure ECG = electrocardiogram LBBB = left bundle branch block RBBB = right bundle branch block

Per cent mortality calculated by formula $\frac{\text{No. of non survivors}}{\text{No. of non survivors + survivors}}$

Other studies however have shown an increased mortality rate associated with complete heart block and BBB whether present prior to an acute MI or developing in association with an acute MI[1, 6]

Cardiogenic shock was the major cause of death in this series of hospitalized patients The electrocardiographic location of the MI did not influence mortality rate since anterior and inferior MIs were associated with similar mortality rates (32.7% and 30.2% respectively Table IV) Pump failure (shock + CHF) was the major cause of death in patients with anterior and inferior MIs (Table V) A larger percentage of patients with anterior MIs (16.8%) compared to inferior MIs (9.4%) died from pump failure Anterior MIs potentially result in the loss of a larger mass of myocardium than do inferior MIs and are often associated with more severe myocardial dysfunction[7]

Inferior MIs occurred in 53 patients and were associated with shock in four patients (Table V) In three of these four patients papillary muscle dysfunction probably contributed to the shock In the fourth patient the inferior MI was associated with a prior anterior MI Isolated inferior MIs without prior anterior MIs and without papillary muscle dysfunction were not associated with shock

The second most common cause of death was external cardiac rupture (17.9% Table V) The incidence of autopsy documented cardiac rupture was 17.9% (10 of 56) in this study in which the autopsy rate was 41% (23 of 56) An additional two patients suffered a ruptured ventricular septum and died postoperatively The inclusion of these two patients brings the total incidence of cardiac rupture causing death to 20.7% Cardiac rupture may have occurred in an additional four patients in whom the clinical signs of cardiac rupture—sudden chest pain and or unconsciousness which is associated with apnea absent peripheral pulses an unobtainable blood pressure and the rapid development of a sinus or junctional bradycardia—were observed but autopsy confirmation was not obtained (Table V)[2] When these four patients are added to the ten patients with autopsy documented cardiac rupture and the two patients with a ruptured ventricular septum the incidence of cardiac rupture in this series becomes 28.6% This is over two and one half times the incidence of cardiac rupture reported in most series and suggests that the elderly dying of acute MI have a higher incidence

26 Sievers, J Cardiac rupture in acute myocardial infarction Geriatrics 21 125 1966
27 Sugiura M., and Okada, R Myocardial rupture in old age Geriatrics 25 130 1970
28 London, R. E., and London, S B Rupture of the heart A critical analysis of 47 consecutive autopsy cases Circulation 31 202, 1965
29 Mogensen, L., Nyquist O., Drinius, E., and Sjogren, A Studies of myocardial rupture with cardiac tamponade in acute myocardial infarction II Electrocardiographic changes, Chest 61 6 1972
30 Van Tassel, R. A., and Edwards, J E Rupture of heart complicating myocardial infarction Chest 61 104 1972
31 Armstrong A., Duncan B., Oliver M F., Julian D G Donald, K. W., Fulton M., Lutz, W., and Morrison S L. Natural history of acute coronary attacks. A community study Br Heart J 34 67 1972
32 Pantridge J F Mobile coronary care Chest 58 229 1970
33 Lown B., and Sidel, V W Duration of hospital stay following acute myocardial infarction, Am. J Cardiol 23 1 1969
34 Gross H. Vaid, A. K., Levine H S and Hasson, J Anticoagulant therapy in myocardial infarction. overview of methodology Am. J Med 52 421 197_
35 Castelli, W P CHD risk factors in the elderly Hosp Pract 11 113 1976
36 Russek, H I., and Zohman, B L. Chances for survival acute myocardial infarction J.A.M.A 156 65 1954
37 Pomerance A Pathology of the heart with and without cardiac failure in the aged, Br Heart J 27 69 1965
38 Pomerance A. The many facets of cardiac pathology Geriatrics 28 110 1973
39 Caird, F I Heart disease in old age Postgrad. Med. 39 408 1963

Copyright Information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner s consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients This consent is given on the condition however that the copier pay the stated per copy fee through the Copyright Clearance Center Inc 21 Congress Street, Salem Mass 01970 617 744 3350 for copying beyond that permitted by Sections 107 or 108 of the U S Copyright Law This consent does not extend to other kinds of copying such as copying for general distribution for advertising or promotional purposes for creating new collective works or for resale

the elderly may be related to the high incidence of coexisting pathological processes which could contribute to pump failure[37, 38] Pathological changes occurring with aging include myocardial fibrosis aortic and mitral valve degenerative changes and calcification senile cardiac amyloidosis and presbycardia[37, 39] The high incidence of myocardial rupture in the elderly may also be a result of the chronic pathological changes that affect the aged myocardium In this sense advanced age is indeed a potent nonmodifiable risk factor that is associated with a high mortality rate[25]

Summary

The history and clinical course of 175 patients aged 70 and older (Group A) with acute myocardial infarction (MI) was studied to determine the hospital mortality rate in this population group and to determine the clinical factors that influenced the hospital mortality rate The mortality rate of a second group of 772 patients below age 70 years (Group B) admitted during the same time period was determined for comparison with the mortality rate in Group A

The hospital mortality rate in Group A (32%) was 3 9 times the hospital mortality rate in Group B (8 2%) Advanced age was associated with a significantly higher mortality rate even when so called good risk patients from Group A were compared with patients in Group B

The major causes of death in this hospitalized group of patients aged 70 and older were shock (33 9%) and cardiac rupture (28 6%) Factors that significantly influenced hospital mortality rate in the elderly group were the development of shock pulmonary edema on chest x ray a clinical diagnosis of congestive heart failure and the development of complete heart block or new bundle branch block during the hospital course

The authors express their grateful appreciation to the Piedmont Hospital Coronary Care Unit nurses for their help in data collection We also wish to thank Drs Robert C Schlant and J Willis Hurst for their constructive comments and Mrs Pat Kirby for her secretarial skills

REFERENCES

1 Cole D R Singian E B and Katz L N The long term prognosis following myocardial infarction and some factors which affect it Circulation 9 321 1954
2 Peel A A F Age and sex factors in coronary artery disease Br Heart J 17 319 1955
3 Norris R M Brandt P W T Caughey D E Lee A J and Scott, P J A new coronary prognostic index Lancet 1 274 1969
4 Williams, B O Begg T B., Semple T., and McGuinness, J B The elderly in a coronary unit Br Med J 2 451 1976
5 Frank C W The course of coronary heart disease factors relating to prognosis Bull. N Y Acad Med 44 900 1968
6. Norris R M Caughey D F Deeming L W Mercer C J and Scott P J Coronary prognostic index for predicting survival after recovery from acute myocardial infarction Lancet 2 485 1970
7 Norris, R M Caughey D E Mercer C J., and Scott P J Prognosis after myocardial infarction six year follow up Br Heart J 36 786 1974
8 Bainton C R., and Peterson D R. Deaths from coronary heart disease in persons fifty years of age and younger N Engl J Med 268 569 1963
9 Oberman A. Jones W B Riley C P Reeves T J Sheffield, L T and Turner M E. Natural history of coronary artery disease Bull N Y Acad Med 48 1109 1972
10 Madias J E Chahine R A Gorlin R and Blacklow D J A comparison of transmural and nontransmural acute myocardial infarction Circulation 49 498 1974
11 Rosenbaum M B., Elizari, M V., Kretz A and Taratuto A L. Anatomical basis of AV conduction disturbances Geriatrics 25 132 1970
12 Rosenbaum M B Intraventricular trifascicular block Heart Lung 1 216 1972
13 Lev M Anatomic basis for atrioventricular block Am J Med 37 742 1964
14 Pell S and D Alonzo C A Immediate mortality and five-year survival of employed men with a first myocardial infarction N Engl J Med 270 915 1964
15 Scheinman M and Brenman B Clinical and anatomic implication of intraventricular conduction blocks in acute myocardial infarction Circulation 46 753 1972
16 Harper R., Hunt D Vohra J., Peter T and Sloman G His bundle electrogram in patients with acute myocardial infarction complicated by atrioventricular or intraventricular conduction disturbances, Br Heart J 37 705 1975
17 Sobel B E Bresnahan G F., Shell W E and Yoder R D Estimation of infarct size in man and its relation to prognosis, Circulation 46 640 1972
18 Page D L. Caulfield J B Kastor J A., DeSanctis, R W and Sanders C A Myocardial changes associated with cardiogenic shock N Engl J Med 285 133 1971
19 Russell R O Hunt D., and Rackley C E Left ventricular hemodynamics in anterior and inferior myocardial infarction Am J Cardiol 32 8 1973
20 Hamby R I Hoffman I Hilsenrath J Aintablian A Shanies S and Padmanabhan V S Clinical hemodynamic and angiographic aspects of inferior and anterior myocardial infarctions in patients with angina pectoris, Am J Cardiol. 34 513 1974
21 Bates R J., Beutler S Resnekov L and Anagnostopoulos, C E. Cardiac rupture—challenge in diagnosis and management Am J Cardiol. 40 429 1977
22 Mundth E D Rupture of the heart complicating myocardial infarction Circulation 46 427 1972
23 Biorck G Mogensen L, Nyquist O Orinius, E and Sjogren A. Studies of myocardial rupture with cardiac tamponade in acute myocardial infarction I Clinical features Chest 61 4 1972
24 O'Rourke M F Subacute heart rupture following myocardial infarction Lancet 2 124 1973
25 Van Montgem J P and Becker A E Developing cardiac rupture as initial sign of acute myocardial infarction Br Heart J 38 1073 1976

Table I Age and sex in 15 patients

	N	Age (yrs)	Mean (yrs)	SD
Total	15	35-72	53 5	10 3
Males	8	41 72	55 0	–
Females	7	35 66	51 9	–

Table II Plasma volume variations

	Pre injection	2 min post injection	30 min post injection
Mean	2,903 ml	3 384 ml	3 005 ml
SD	720	792	366
P<	0 001 (pre vs 2 min)	0 001 (2 min vs 30 min)	
	N S (pre vs 30 min)		

for capillary fluid exchanges calculated as COP LVEDP is observed (Table IV) decreasing from a mean 8 4 mm Hg to a slightly negative gradient of –0 3 mm Hg Forty four per cent of this shift in gradient is accounted by the changes in COP (3 8 of 8 7 mm Hg)

Discussion

It is well recognized that an intravascular bolus injection of contrast media may precipitate acute pulmonary edema[5, 9] The observed expansion in plasma volume at two minutes after injection is consistent with other similar studies[2, 3] and represents an acute plasma expansion of 8 to 10 ml for each milliliter of hyperosmolar solution injected

The LVEDP elevation is well recognized as a major cause of pulmonary edema[18, 19] Almost a century ago Starling[2] suggested that intravascular colloids promote fluid absorption from the interstitial space at the microcirculatory level Guyton and associates and other workers[22, 23] subsequently presented quantitative evidence to substantiate the importance of the relation between left atrial pressure and plasma protein concentration on the development of pulmonary edema Since the more extensive availability of instruments for clinical measurement of COP the clinical importance of oncotic pressure in the evolution of pulmonary edema has been better defined[14] Stein and co workers[2, 25] presented evidence for pulmonary edema formation in the absence of left ventricular failure if the oncotic pressure is significantly decreased Da Luz and associates[12] showed that pulmonary edema may appear in the absence of a significant increase of the left ventricular filling pressure after acute myocardial infarction if the oncotic pressure is significantly decreased leading to an almost abolished gradient for capillary fluid exchanges In the critically ill patient the gradient for capillary fluid exchanges represents a much better predictor of pulmonary edema than the isolated measurement of LVEDP an abolished gradient representing a major risk of pulmonary edema whatever the LVEDP[10, 11, 6, 26] The hemodilution hypervolemia induced by a bolus injection of contrast media increases the LVEDP and simultaneously decreases the COP level Those changes invert (positive to negative) the gradient for capillary fluid exchanges resulting in a pulmonary edema prone situation It should be noted however that the relative importance of the decrease in COP and the increase in LVEDP varies from patient to patient in relation to the magnitude of the LVEDP changes The variations in COP are relatively fixed and determined by the volume changes

We conclude from this study that after a bolus injection of contrast media the total intravascular pressure changes predisposing to pulmonary edema are almost equally shared by the hydrostatic and oncotic pressure changes These findings further clarify the mechanism of pulmonary edema induced by contrast media

Summary

Angiographic contrast media are known to induce alterations in cardiovascular dynamics which may result in acute pulmonary edema The risk of pulmonary edema was previously shown to be negatively correlated to the level of colloid oncotic pressure (COP) It was also shown that the gradient between COP and left ventricular end diastolic pressure (LVEDP) represents a better predictor of pulmonary edema than does LVEDP alone The present report evaluates the effects of a bolus injection of contrast media on those pressures as predisposing factors for pulmonary edema

Our data are based on 15 unselected patients admitted for coronary angiography The plasma volume increased by 16 5% (2 903 to 3 384 ml) a

Effects of angiographic contrast media on colloid oncotic pressure

Martin Morissette M D
Roger M Gagnon M D
Jacques Lamoureux M D
Jean Lemire M D
Montreal Quebec Canada

Left ventriculography requires a rapid injection of hyperosmolar contrast material into the arterial side These agents are known to decrease myocardial contractility [1,2] and cause a rapid increase in blood volume and cardiac output The general risk of pulmonary edema is 0 08% in all angiographic procedures [3,6] This risk may be significantly higher in patients with a compromised ventricular function [7,8] The problem of pulmonary edema has been attributed to an increased circulating blood volume and filling pressure The importance of acute hypervolemia on the oncotic pressure of plasma and edema formation even if suspected remains to be evaluated and quantified It is recognized that COP is inversly correlated to the risk of pulmonary edema [ ] Also it has been demonstrated that the risk of pulmonary edema is better predicted by the gradient for capillary fluid exchanges represented by the difference between colloid oncotic pressure (COP) and left ventricular end diastolic pressure (LVEDP) than by LVEDP alone In the present study the effects of a bolus injection of contrast media on COP and on the COP LVEDP gradient are examined

Material and methods

The group consisted of 15 unselected patients admitted for elective coronary angiography It included eight males and seven females with a mean age of 53 5 years (Table I) The patients were studied in the fasting state and received 10 mg diazepam orally as premedication From 40 to 60 ml of meglumine diatrizoate (Renographin 76%) was injected in 2 5 to 4 seconds for the left ventricular angiogram

A single injection of radioiodinated human serum albumin (RI[1] [3]SA) was used for determination of the three sequential plasma volumes [1] They were measured before at two and at 30 minutes following the injection of contrast material

COP was measured on plasma by the use of a transducer membrane system representing a modification of the technique of Prather [15] Weil [16] [ ] and their colleagues Arterial blood was obtained at the same time as plasma volume sampling

Results

The sequential changes in plasma volume following injection of contrast media are summarized in Table II A 16.5% increase in plasma volume is observed at two minutes A return towards normal values is found at 30 minutes although a slight non significant elevation still remains compared to the baseline

The COP response is shown in Table III Contrasting the increase in plasma volume a significant fall in plasma COP (16 2% $P < 0\,001$) is observed In 30 minutes the COP has returned to the control level

The end diastolic pressure significantly increases (Table III) at two minutes in parallel with the changes in plasma volume

A significant shift ($P < 0\,001$) of the gradient

From Notre Dam Hospital U ersity of M ntreal, Montreal, Quebec Can da

Recei ed f r publ cation Feb 21 19 9
A cepted f r publicati n M y 14 1979

Reprint requests Martin M rissett M D N tre D m Hosp t l 1560 Sherbrooke E st Montreal, Q bec C n da H 1 4K8

000? 8 03/80/090319 + 04$00 40 0 1980 The C V Mosby Co

osmotic and pulmonary artery wedge pressure in patients with acute myocardial infarction Circulation **51** 350 *1975*

13 Smith, S J Hagemeijer F Gerbrandy J and Esseveld M R The significance of colloid osmotic pressure and pulmonary capillary wedge pressure in pulmonary edema secondary to acute myocardial infarction in man Neth J Med **19** 118 1976

14 Powsner E R and Raeside D E Hematologic and radioisotope dilution procedures *in* Diagnostic Nuclear Medicine New York 1971 Grune & Stratton Inc p 293

15 Prather J W Gaar K A and Guyton A C Direct continuous recording of plasma colloid osmotic pressure of whole blood J Appl Physiol **24** 602 1968

16 Weil M H Morissette M Michaels S Bisera J Boycks E Shubin H and Jacobson E Routine plasma colloid osmotic pressure measurements Crit Care Med **2** 229 1974

17 Bisera J Weil M H., Michaels S Bernardo A and *Stein B An Oncometer* for clinical measurement of colloid osmotic pressure of plasma Clin Chem **24** 1586 1978

18 Forrester J S Diamond G McHugh T J and Swan H J C Filling pressures in the right and left sides of the heart in acute myocardial infarction A reappraisal of central venous pressure monitoring N Engl J Med **285** 190 1971

19 Kostuk, W Barr J W Simon A L and Ross J Correlations between the chest film and hemodynamics in acute myocardial infarction Circulation **48** 624 1973

20 Starling E K On the absorption of fluids from the *connective tissue spaces* J Physiol (Lond) **19** 312 1896

21 Guyton A C and Lindsey A W Effect of elevated left atrial pressure and decreased plasma protein concentration on the development of pulmonary edema Circ Res **7** 649 1959

22 Gaar A K Taylor A E and Owens L J Effect of capillary pressure and plasma protein on development of pulmonary edema Am J Physiol. **213** 79 1967

23 Cooper J D Maeda M and Lowenstein E Lung water accumulation with acute hemodilution in dogs J Thorac. Cardiovasc Surg **69** 957 1975

24 Stein L Beraud J J Cavanilles J Da Luz P Weil, M H and Shubin H Pulmonary edema during fluid infusion in the absence of heart failure J.A.M.A **229** 65 *1974*

25 Stein L Beraud J J Morissette M Da Luz P Weil, M H and Shubin H Pulmonary edema during volume infusion Circulation **52** 483 1975

26 Morissette M Weil M H Shubin H and Liu, V Significance of changes in colloid osmotic pressure in critically ill patients First World Congress on Intensive Care London 1974 Scientific Abstracts I McA Ledingham *p* 141

27 Morissette M Weil, M H and Shubin H Reduction in colloid osmotic pressure associated with fatal progression of cardiopulmonary failure Crit Care Med **3** 115 1975

28 Morissette M P Colloid osmotic pressure Its measurement and clinical value Can Med Assoc J **116** 897 1977

IMPORTANT
INFORMATION FOR AUTHORS

All manuscripts for the AMERICAN HEART JOURNAL should be sent to

Dean T Mason M D
Section of Cardiovascular Medicine
University of California
School of Medicine
Davis California 95616

Table III COP and LVEDP (mm Hg) responses after constrast ventriculography

Case	Colloid oncotic pressure			LVEDP	
	Pre	2 min	30 min	Pre	2 min
1	26.1	23.0	24.6	12	15
2	24.8	20.1	28.2	14	20
3	23.8	18.6	[illegible]	12	15
4	22.4	19.8	25.1	10	17
5	24.3	20.9	23.6	15	20
6	24.7	21.4	24.1	15	15
7	23.0	20.4	25.0	22	25
8	22.4	19.4	22.5	15	22
9	20.8	17.5	20.4	8	15
10	22.8	20.0	21.0	10	18
11	28.3	23.8	[illegible]	17	20
12	24.7	19.3	22.7	16	30
13	23.8	17.2	21.8	10	15
14	17.9	14.5	16.4	33	33
15	20.9	17.5	20.1	17	18
Mean ± SD	23.4 ± 2.4	19.6 ± 2.3	22.7 ± 2.6	15.1 ± 5.9	19.9 ± 5.4
P	Pre vs 2 min: < 0.001	2 min vs 30 min: < 0.001	Pre vs 30 min: NS	< 0.001	

two minutes after injection of a 50 c.c. bolus of meglumine diatrizoate (Renographin 76%) and had returned towards normal at 30 minutes. In parallel the COP decreased from 23.4 ± 2.4 to 19.6 ± 2.3 mm Hg ($P < 0.001$) to return the 22.7 ± 2.6. The COP LVEDP gradient decreased by 8.7 mm Hg (8.4 to −0.3, $P < 0.001$). Such a gradient was well within the danger zone of pulmonary edema. These findings further clarify the mechanisms of pulmonary edema induced by contrast media.

Table IV COP LVEDP gradient changes (mm Hg)

	COP LVEDP changes		COP changes
	Pre injection	2 min post injection	Pre injection −2 min post injection
Mean	8.4	−0.3	−3.8
SEM	1.9	1.8	0.3
P<	0.001		

REFERENCES

1. Gootman N., Rudolph A. M. and Buckley N. M. Effects of angiographic contrast media on cardiac function. Am. J. Cardiol. 25:59, 1970.
2. Crelinsten G., Fallen E., Fenton R., Marpole D. and Sniderman A. The significance of early changes of positive and negative dP/dt following contrast ventriculography. Cathet. Cardiovasc. Diagn. 2:337, 1976.
3. Isen, L. T., Kaplan M. A., Evans M. J. and Nickel E. D. Effects of concentrated contrast media during angiography on plasma volume and plasma osmolality. AM HEART J 69:154, 1965.
4. Brown A. K., Epstein E. J., Coulshed N., Clarke J. M. and Doukas, N. G. Haemodynamic changes after angiography. Br. Heart J 31:233, 1969.
5. Shehadi, W. H. Adverse reactions to intravascularly administrated contrast media. A comprehensive study based on a prospective survey. Am. J. Roentgenol. 124:145, 1975.
6. Bourassa, M. G. and Noble J. Complication rate of coronary arteriography. A review of 5250 cases studied by a percutaneous femoral technique. Circulation 53:106, 1976.
7. Malins, A. F. Pulmonary edema after radiological investigation of peripheral occlusive vascular disease. Adverse reaction to contrast media. Lancet 1:413, 1978.
8. Roback D. L. Caution with contrast media. Lancet 1:1153, 1978.
9. Aps C. Pulmonary edema following translumbar aortography. Proc. R. Soc. Med. 68:766, 1975.
10. Rackow E. C., Fein I. A. and Leppo J. Colloid osmotic pressure as a prognostic indicator of pulmonary edema and mortality in the critically ill. Chest 72:709, 1977.
11. Weil, M. H., Henning R. J., Morissette, M., and Michaels, S. Relationship between colloid osmotic pressure and pulmonary artery wedge pressure in patients with acute cardiorespiratory failure. Am. J. Med. 64:643, 1978.
12. Da Luz P., Shubin H., Weil, M. H., Jacobson E., and Stein L. Pulmonary edema related to changes in colloid



Fig 1 Lymphangiogram of left ventricle from normal dog

Table I Percentage of left ventricular surface area occupied by lymphatic vessels data obtained by grid and point counts

Protocol	*N*	*Mean point count*	*SEM*	*Surface area (%)*	*P (differ from normal)*
Normal dog left ventricle	6	1 64	0 11	6 6%	
Coronary occlusion—ischemic zone	7	90	0 06	3 6%	< 0 001
Coronary occlusion—non infarcted zone	7	2 81	0 22	11 2%	< 0 001
Hyaluronidase—normal dog	6	3 45	0 18	13 8%	< 0 001
Hyaluronidase—infarcted zone	7	5 22	0 34	20 9%	< 0 001
Hyaluronidase—noninfarcted zone	7	2 65	0 08	10 6%	< 0 001
Bioassay of toxic lymph	5	4 8	0 2[illegible]	[illegible]	< 0 001
Spontaneous arrhythmias	3	1 19	0 11	4.8%	NS

fivefold magnification using a 0 1 mm focal spot Seimens tube and exposure factors of 50 kV 0 01 sec and 30 mA With this technique it was possible to visualize 50 to 80 micron lymphatic vessels

2 Hyaluronidase administration In six normal dogs and in seven dogs beginning 20 minutes prior to coronary occlusion hyaluronidase (Sigma Chemical St Louis Mo) was administered intravenously in a dose of 500 I U every 6 hours for a total of four or five doses

3 Cardiac lymph collection In five live dogs, the chest was opened through a left thoracotomy incision in the third intercostal space and the pericardium was incised parallel to the phrenic nerve Evans Blue (0 5 ml) was injected subendocardially at the left ventricular apex to allow visualization of the lymphatics The main cardiac

Cardiac lymph and lymphatics in normal and infarcted myocardium

Laszlo Szlavy M D
Douglass F Adams M D
Norman K Hollenberg M D
Herbert L Abrams M D
Boston Mass

Despite sporadic interest in the lymphatic drainage of the myocardium the possibility that disordered lymphatic function contributes to tissue destruction following coronary artery occlusion has not been systematically examined During a study on the normal coronary lymphatic drainage we found that hyaluronidase had a striking influence on lymphatic visualization in the heart[1] Because hyaluronidase also has a clear influence on the evolution of myocardial necrosis after coronary occlusion[2,3] and because an unequivocal explanation for the mechanism by which hyaluronidase induces the salutary response is not available we undertook a systematic investigation into the lymphatic drainage of normal and infarcted myocardium and the impact of hyaluronidase on both The results are consistent with an important role of altered lymphatic drainage in the evolution of myocardial infarction and with a mechanism of hyaluronidase action which includes better sustained lymphatic drainage following myocardial infarction perhaps facilitating removal of high molecular weight toxic substances such as lysosomes from the ischemic myocardium

Methods and materials

Studies were performed in 48 mongrel dogs of either gender weighing about 20 kilograms Anesthesia was induced and maintained with sodium pentobarbital (30 mg /kg) and ventilation was maintained through an endotracheal tube with a Harvard respirator which provided 200 to 300 c c of room air/breath at a rate of 18 to 20/minute

Catheters were placed in the aorta from the right femoral artery for blood pressure monitoring and in the inferior vena cava from the right femoral vein for maintaining anesthesia In experiments during which the coronary artery was occluded without thoracotomy an additional catheter was placed via the left femoral artery in a superselective position in the left anterior descending or left circumflex coronary artery Coronary occlusion was accomplished in this way to avoid the possibility of venous or lymphatic obstruction which may occur when ligation is the method used to occlude the coronary arteries The artery was occluded with either a piece of Gelfoam (5 × 1 mm) or the tip of radiopaque polyethylene catheter using a modification of a technique described from this laboratory by Cohen and Eldh[4] All animals were killed at 24 hours and cardiac lymphangiography was performed immediately after death

1 Technique for cardiac lymphangiography Lymphatic vessels in the apical portion of the left ventricle were cannulated postmortem with a 30 gauge Becton Dickinson lymphangiography set using a 2 5 magnification lens The contrast agent utilized was made by adding 30 grams of barium sulfate to 3 to 5 ml of Iodamide 420 (Bracco Milan Italy) Five drops of food coloring were added to allow different colors for each lymphatic vessel The contrast agent was injected under gentle manual pressure until the lymphatic vessels were filled The heart was x rayed with

From the Department of Radiology Harvard Medical School and Fete Bent Brigham Hospital Boston Mass

Supported in part by United States Public Health Service Grants No HL 03832 GM18674 and HL 70895

Received for publication March 5 1979

Accepted for publication Apr 24 1979

Reprint requests Douglass F Adams M D Dept of Radiology Harvard Medical School, 25 Shattuck St Boston Mass. 02115

0002-8 03/80/090323 + 09$00 90 0 © 1980 The C V Mosby Co



Fig 3 Lymphangiogram from dog pretreated with hyaluronidase Coronary arteries were patent in the dog

cm served as a single basic unit as it corresponded to 1 cm of ventricular myocardium (fivefold magnification was used for filming the lymphangiogram) Because of the 1 cm separation between the lines 25 crossings were present in each basic unit Each 1 cm on the grid corresponded to 2 mm of the venticular myocardium A point was counted whenever a crossing coincided with a vasualized lymph vessel in the lymphangiogram This approach provides *not a count* of lymphatic vessels but rather an index of their volume relative to that of ventricular myocardium The entire left ventricular surface was evaluated whenever point counts were obtained Following coronary occlusion the entire infarcted or noninfarcted zones were counted

Mean values have been presented with the standard error of the mean as the index of dispersion Statistical analyses were performed where appropriate with the Student t test The null hypothesis was rejected when P was less than 0 05

Results

1 Effect of *coronary* occlusion on lymphan*giograms* A typical normal myocardial lymphangiogram is shown in Fig 1 In the normal myocardium there was 1 64 ± 0 11 points/cm ventricle equivalent to 6 6% of the ventricular area (Table I) The variation from animal to animal was small as evidenced by a coefficient of variation of only 16 4%

Acute coronary occlusion induced striking statistically significant changes in the visualization of lymphatics on lymphangiography in both the infarcted zone and in the surrounding noninfarcted tissues In the infarcted zone (Fig 2 Table I) there was a marked reduction in the number of lymphatics visualized (0 90 ± 0 06 points/cm² ventricle 3 6% of ventricular area $p < 0.001$ vs normal) Conversely the noninfarcted zone showed a considerable increase in lymphatic visualization (2 81 ± 0 22 points/cm² ventricle 11 2% of ventricular area $p < 0.001$ vs normal)

2 Effect of hyaluronidase on lymphangiograms Hyaluronidase augmented myocardial lymphatic visualization in the normal dog In six normal dogs lymphatic density following hyaluronidase pretreatment was increased significantly (3 45 ± 0 18 13 8% of ventricular area $p < 0.001$ vs untreated normal myocardium) (Fig 3)

Hyaluronidase pretreatment resulted in improved visualization of lymphatics in the infarcted zones (5.22 ± 0 34 points/cm² ventricle 20 9% of ventricular area $p < 0.001$ vs

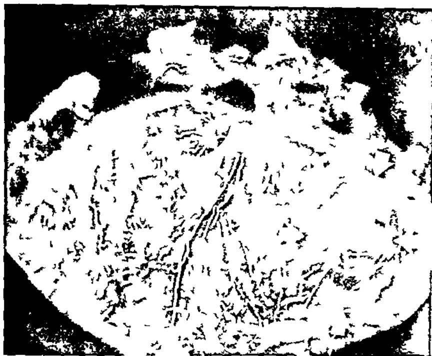


Fig 2 Lymphangiogram from dog with myocardial infarction following coronary occlusion *The arrows* indicate the ischemic zone

lymphatic trunk which measures approximately 1.5 mm in diameter was cannulated 2 to 3 cm above the left atrial appendage just before it enters the cardiac lymph node The catheteriza tion was accomplished with an angiocatheter (Intercath 22 gauge size Deseret Co Sandy Utah) after ligation of the lymphatic trunk to engorge the vessel

Lymph was collected in open tubes during free flow or with slight negative pressure for 2 hours prior to coronary occlusion and in 2 hour collec tions for 4 to 5 hours following coronary occlu sion Samples were collected on ice spun to remove visible blood cells and were frozen imme diately for bioassay the following day in four of the five experiments In the remaining experi ment the lymph was bioassayed immediately after the collection on ice

4 Bioassay of myocardial lymph The lymph samples were assayed in five normal dogs The left coronary artery was catheterized as described above the blood pressure and the ECG were continuously monitored

First the effect on the electrocardiogram of 1 0 ml of normal saline injected into the left coro nary artery of normal animals was evaluated for 10 minutes as a control As a second control lymph collected prior to coronary occlusion was injected as a 1 0 ml bolus and blood pressure and the electrocardiogram were monitored for 60 to 120 minutes Lymph obtained during the first 2 hours following coronary occlusion was then injected into the coronary artery of normal stable dogs and the animals were observed for 60 to 120 minutes Finally lymph collected during the second 2 hour interval following coronary occlusion was injected into the coronary artery of normal stable dogs and the animals were observed for an additional 4 to 6 hours

Following termination of the experiment lym phangiograms were obtained in all animals

In an additional three normal dogs with cardiac arrhythmias induced by placement of an electro magnetic flow meter probe around the coronary artery but in which no injections of any agent into the coronary artery were performed lym phangiograms were obtained to assess the contri bution of arrhythmias to lymphangiographic fea tures

5 Methods of analysis A grid was prepared to serve as an overlay on the fivefold magnified lymphangiograms allowing quantification of vi sualized lymphatics The grid considered of lines drawn at right angles 1 cm apart Each 5 × 5

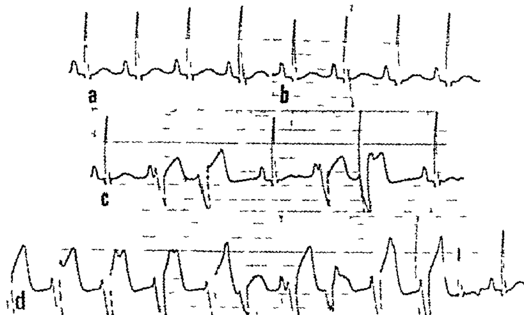


Fig 5 ECG changes in a normal dog following injection of saline *(a)* normal myocardial lymph *(b)* lymph obtained during the first 2 hours following coronary occlusion *(c)* and lymph obtained during the second ? hour interval following coronary occlusion *(d)*

occlusion The better sustained lymphatic system may be a cause or a consequence of favorable hyaluronidase influence on the course of tissue destruction If it were causal it might be assumed that the preserved lymphatics drain toxic material from the affected myocardium following coronary occlusion Our fourth observation is that indeed a factor toxic to the heart is found in lymph draining the myocardium following coronary occlusion

These observations permit three major lines of investigation to be integrated into a single conceptual framework An elegant series of studies has already implicated membrane damage and lysosomal enzyme release as participants in the development of tissue necrosis with ischemia [1] A second line of investigation has provided unequivocal evidence that hyaluronidase reduces myocardial necrosis following coronary occlusion but with no clear indication as to what the protective mechanism may be [2,12,19] Studies on lymphatic drainage from the hypoxic or ischemic heart have [illegible] that quantitatively important change [illegible] lymph flow occur and that obstruction [illegible] ic outflow has a pernicious influence on [illegible] of myocardial necrosis but have a[illegible] to define their over all contribution [illegible] volution of myocardial infarction [19] [illegible] king hypothesis is that lymphatic drainage is a determinant of tissue survival after coronary occlusion because toxic products possibly the products of damaged myocardial cells are removed via this route

What species of molecule is most likely to be drained primarily by lymphatics? For molecules of a size too large to allow easy access to the bloodstream via the blood capillary wall an important avenue of escape is likely to occur via the lymphatics Consistent with this concept three studies have demonstrated that enzymes such as creatine phosphokinase appear in myocardial lymph well before their concentration in blood rises following coronary occlusion [3,14]

Attention has been focused primarily on membrane disruption and evidence that lysosomal enzyme release occurs when the membranes become abnormal with considerably less attention paid to the role of the enzymes once they are released Certainly their local concentration and thus their toxicity must depend not only on their rate of release but also on the rate at which they are degraded or carried away Thus the transport and behavior of the enzymes and the compartments involved in their transport such as the interstitial space lymphatic vessels or coronary venous blood must also be considered Viewed in the perspective of our lymphangiograms following coronary occlusion perhaps it is not surpr-



Fig 4 Lymphangiogram obtained from dog pretreated with hyaluronidase and then subjected to coronary occlusion *The arrows* indicate the ischemic zone

untreated infarction) (Fig 4) There was no difference in the lymphatic density in the non infarcted zone in hyaluronidase pretreated and untreated dogs with coronary occlusion (2 65 ± 0 08 vs 2 81 ± 0.22)

3 Effect of cardiac lymph injections into the coronary arteries Saline and normal lymph injected into the coronary arteries induced no electrocardiographic changes (Figs 5*A* and 5*B*) Lymph collected during the first two hours following coronary occlusion induced relatively minor and transient electrocardiographic changes (Fig 5*C*) Lymph collected 2 to 4 hours following coronary occlusion induced in each case malignant arrhythmias in the normal dogs (Fig *5D)* In all cases the arrhythmias were delayed in onset first becoming evident in 10 to 15 minutes following injection and becoming progressively more severe Multifocal ventricular premature contractions were followed by ventricular tachycardia and ventricular fibrillation within 35 to 90 minutes following injection in three of the five dogs In the other dogs used for bioassay prolonged bouts of ventricular tachycardia subsequently reverted to normal rhythm with ST segment elevation > 3 mm at 6 hours following the injection of toxic lymph when the experiment was terminated

Lymphangiography demonstrated an increase in the number and size of visualized lymphatics present in each of the five dog hearts which had received toxic lymph injections into the coronary artery (4.3 ± 0.27 points/cm ventricle 17.2% of ventricular area $p < 0\,001$ vs normal) (Fig 6) No significant increase in lymphatic density could be detected in the three dogs with cardiac arrhythmias induced by mechanical stimulation (1 19 ± 0 11 points/cm ventricle 4.8% ventricular area p = NS)

Discussion

There are four new and probably related observations in this study which may shed light on the pathogenesis of progressive tissue destruction following coronary artery occlusion First a remarkable reduction in visualized lymphatic channels from ischemic myocardium occurs within 24 hours of coronary occlusion well before the disappearance of lymphatic vessels can be accounted for on the basis of coagulation necrosis Second hyaluronidase has a striking influence on the lymphatic vascular tree of the normal heart Third sustained integrity of the myocardial lymphatic system parallels the reduction in myocardial tissue destruction associated with hyaluronidase administered prior to acute coronary

necrosis one might anticipate substantial release of potassium and other small ions or organic moieties along with the intracellular protein re lease Detailed studies on the character of lymph draining the ischemic heart[27] and kidney[33] have detected little or no change in potassium or protein concentration The simplest explanation would appear to be that blood flow in the ischemic zones while markedly reduced, is still adequate to wash away the small molecules which easily diffuse into capillaries Whatever the explanation potassium and other small ions are not likely candidates as the toxic factor

The role of lymphatics in the evolution of tissue necrosis following coronary occlusion in the pro tective effect of hyaluronidase and in the clear ance of toxic factors from ischemic myocardium clearly requires more detailed evaluation Per haps the highest priority should be placed on identifying and characterizing the toxic material or materials a task which should be facilitated by what is clearly a very high concentration in the draining lymph As little as 0 5 ml injected into a healthy dog s coronary artery was lethal

Summary

Cardiac lymphangiography was applied to 29 normal dogs (ND) and 14 dogs following acute coronary occlusions In five of the ND lymph collected from infarcted dogs was selectively injected into the coronary artery prior to the lymphangiogram In ND the lymphatic density (LD) was 6 6% ventricular area (VA)

Acute coronary occlusion induced a change in the LD The infarcted zone registered a decrease in LD (3 6% of VA p < 0 001 vs ND) Hyaluroni dase increased LD in normal dogs (13 8% of VA p < 0 01 vs ND) Hyaluronidase pretreatment increased the LD in infarcted myocardium (20 9% of VA p < 0 001 vs non treated infarcts) No difference was seen between uninfarcted areas of treated and nontreated animals (10 6% vs 11 2% of VA) Lymph was collected from cardiac lym phatics in five dogs before and after coronary occlusion When selectively injected into coro nary arteries of ND post infarct lymph induced ECG changes of ischemia arrhythmias and increased the LD (14 6% VA p < 0 001 vs ND) The results suggest (1) Cardiac lymphatics are altered in the uninfarcted and infarcted zones following coronary occlusion (2) Hyaluronidase preserves the lymphatic density in infarction (3) Lymph collected from zones of infarction is toxic

REFERENCES

1 Szlavy L Hollenberg N K Adams D F and Abrams, H L The cardiac lymphatic system and its role in myocardial infarction Proceedings of the Association of University Radiologists 26th Annual Meeting May 14 1978

2 Maroko P R Libby P Bloor C M Sobel B E and Braunwald E Reduction by hyalurodinase of myocardial necrosis following coronary artery occlusion, Circulation 46 430 1972

3 Hillis L D Askenazi J Braunwald E Radvany P Muller J E, Fishbein M C and Maroko P R Use of changes in the epicardial QRS complex to assess interventions which modify the extent of myocardial necrosis following coronary artery occlusion Circulation 54 591 1976

4 Cohen M V and Eldh P Experimental myocardial infarction in the closed chest dog Controlled production of large or small areas of necrosis AM HEART J 82 79? 1973

5 deDuve C and Wattiaux R Functions of lysosomes, Ann Rev Physiol 28 435 1966

6 Janoff A and Zweifach B W Production of inflammatory changes in the microcirculation by cationic proteins extracted from lysosomes J Exp Med 120 747 1964

7 Brachfeld N Maintenance of cell viability Circulation 39(Suppl IV) ?02 1969

8 Weissman G Corticosteroids and membrane stabilization Circulation 53(Suppl I) 171 19 6

9 Lefer A M and Okuda M Mechanisms of glucocorticoid protection in experimental myocardial ischemia in Pathophysiology and Therapeutics of Myocardial Ischemia edited by A M Lefer C J Kelliher and M J Rovetto Jamaica N Y 1977 Spectrum Publications pp 413-419

10 Weissmann G Hoffstein S Gennaro D and Fox A C Lysosomes in ischemic myocardium with observations on the effects of methylprednisolone *in* Pathophysiology and Therapeutics of Myocardial Ischemia edited by A M Lefer G J Kelliher M J Rovetto Jamaica, N Y 1977 Spectrum Publications p 367

11 Brachfeld N Metabolic cellular interrelationships during myocardial ischemia *in* Pathophysiology and Therapeutic of Myocardial Ischemia edited by A M Lefer G J Kelliher and M J Rovetto Jamaica N Y 1977 Spectrum Publications p 381

12 MacLean D Fishbein M C Maroko P R and Braunwald E Hyaluronidase induced reductions in myocardial infarct size Science 194 199 19 6

13 Braunwald E and Maroko P R The use of hyaluronidase and hydrocortisone in the reduction of myocardial infarct size following coronary occlusion Acta Med Scand 587(Suppl) 169 1976

14 Kloner R A Fishbein M C Maclean D Braunwald E and Maroko P R Effect of hyaluronidase during the early phase of acute myocardial ischemia An ultrastructural and morphometric analysis Am J Cardiol 40 43, 1977

15 Hillis L. D., Askenazi J Braunwald F Radvany P Muller J E Fishbein M C and Maroko P R Use of changes in the epicardial QRS complex to assess interventions which modify the extent of myocardial necrosis following coronary artery occlusion Circulation 54 591 1976

16 Hillis L. D., Askenazi J Braunwald F and Maroko, P

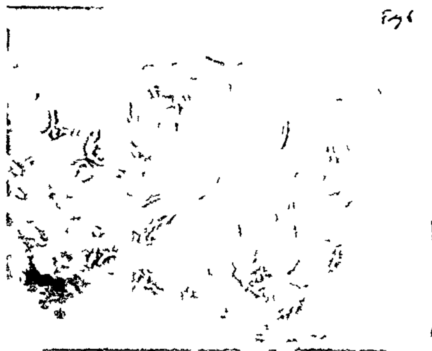


Fig 6 Lymphangiogram of left ventricle in a normal dog following the introduction of toxic lymph into the coronary artery

ing that lysosomal enzyme content of lymph following coronary occlusion was increased but that the increase was disappointingly modest An unstated premise in such studies is that the interstitium of the infarcting zone communicates freely with the draining lymphatic trunks a premise which now seems unlikely

How does hyaluronidase act to modify myocardial infarction? A number of suggestions including reduction of interstitial edema facilitation of perfusion via collateral blood flow and enhanced delivery of critical substrates through the interstitium have been made

Among the suggestions made the possibility that hyaluronidase might exert its salutary effect at least in part by increasing the washout of toxic metabolites has been raised but no direct evidence concerning this possibility was offered Some insight may be gained through close examination of the specific actions of hyaluronidase and the normal physiology of its substrate Hyaluronic acid is a viscous hydrophilic mucopolysaccharide of the connective tissue ground substance which holds the cells in its jelly like matrix by its viscosity In model systems of isolated proteoglycans the polysaccharide network has a negligible effect on the distribution and diffusion of oxygen water and sugars At physiological hyaluronic acid concentrations there is however measurable retardation in the diffusion of molecules as large as plasma proteins presumably because of steric restriction Hyaluronidase apparently facilitates diffusion of large molecules by enhancing the probability that a particle finds a path in the network through which it can move

From this analysis the possibility that hyaluronidase influences myocardial infarction by facilitating the delivery of small molecular weight substrates or oxygen seems less likely than that the diffusion of larger molecules such as protein is influenced critically Consistent with that action hyaluronidase has been documented as increasing lymphatic flow after intravenous injection in the dog[3]

What is the toxic substance likely to be? Because of normal lymphatic function toxic proteins perhaps lysosomal enzymes are likely candidates No direct evidence from this study is as yet available because it was necessary to utilize all of the small volumes of lymph collected for the bioassay to toxicity With the well-documented disruption of cell membranes which occurs during

Effects of circulatory arrest and rewarming on regional blood flow during surface-induced hypothermia

Judy Y Su, Ph D
David W Amory, Ph D , M D
Murray P Sands
H Mohri M D Dr Med Sci
Seattle Wash

Although intensive research efforts have clarified many aspects of hypothermic physiology the distribution of regional blood flow has remained obscure However the relatively recent development of a technology based on the use of nonrecirculating radioactive microspheres has made it possible to simultaneously determine regional blood flow throughout the body In a previous communication[24] we reported on the changes in distribution of cardiac output regional blood flow and vascular resistance during the cooling phase of a method of deep surface induced hypothermia developed in our laboratory and used as an adjunct for the correction of congenital cardiac defects in infants[2 ... 24] This report is intended to demonstrate the effects of induced circulatory arrest on regional blood flow and blood flow distribution during the rewarming phase of surface hypothermia

Materials and method

A detailed description of the operative procedure microsphere administration and radionuclide counting techniques has been provided in our previous report In summary catheters were inserted into the inferior vena cava abdominal aorta and left ventricle of 4 to 7 kg monkeys (*Macaca mulatta)* three days prior to the study On the day of the experiment control (awake) determinations were done Then the animals were anesthetized and surface cooled by our method[12 14] which includes the use of deep ether anesthesia in 100% O_2 artificial ventilation maintained at normal levels for normothermia so as to gradually induce respiratory alkalosis during cooling and the administration of 10 c c /kg of low molecular weight dextran (10% in D W) between 35° and 25° C during cooling

Five animals were cooled to 20° C rectal temperature maintained for 30 minutes and rewarmed by floating the animal on a plastic sheet over warm water (40° C) Another group of four animals were similarly cooled opened by sternotomy and a 30 minute period of circulatory occlusion was induced by crossclamping the cavae pulmonary artery and aorta Cardioplegia was accomplished by injecting 10 c c of Young's Solution* proximal to the aortic crossclamp Resuscitation was accomplished by manual cardiac massage and the administration of 300 mg of calcium chloride to neutralize the Young's Solution Defibrillation when necessary was by 50 volt AC electroshock Rewarming was started at the time of massage

At the end of each experiment the animal was exsanguinated and the major organs were removed weighed and placed in plastic vials for measurement of radioactivity The remainder of

From th Dep tm nts f Anesthes ology and Surg ry School of Medicine Uni rsit f Washingt n Seattle

This study was upported b g nts from the Am ri an Heart Association of Washingt n Nos U S P H S GM01160 nd NIH NL119?03
Received for publ tio n Apr 9 1979
Accepted for public t n Jul 1979

Reprint requests Judy Y Su Ph D Dept of Anesthesiology RN 10 School of Med cin University f Wa hington Se ttle W h 9819

*Young's Sol t on conta ns 0.81 gm of potass um citrate 2.46 gm of magnes um sulfate 0.001 gm of neost gmine methyl sulfate and suff ci nt w ter to make 100 ml pH is adjusted to 7.4 with NaHCO

0002-8703/80/090332 + 09$00.90/0 © 1980 The C V Mosby Co

R The influence of the time interval between coronary artery occlusion and the administration of hyaluronidase on salvage of ischemic myocardium in dogs Circ Res 41 76 1977
17 Rovetto M J Effect of hyaluronidase and methylprednisolone on myocardial function glycose metabolism and coronary flow in the isolated ischemic rat heart Circ Res 41 373 1977
18 Askenazi J., Hillis, L. D Diaz F E Davis M A Braunwald E and Maroko P R The effects of hyaluronidase on coronary blood flow following coronary artery occlusion in the dog Circ Res 40 566 1977
19 Maroko P R Effect of hyaluronidase on infarct size Pathophysiology and Therapeutics of Myocardial Ischemia 22 493 1977
20 Kline I K Miller A J Pick R and Katz L N The effects of chronic impairment of cardiac lymph flow on myocardial reactions after coronary artery ligation in dogs AM HEART J 68 515 1964
21 Miller A J., Ellis, A and Katz L. N Cardiac lymph Flow rates and composition in dogs Am J Physiol 36 63 1964
22 Ullal S R Kluge T H Kerth W J and Gerbode F Flow rates and composition of cardiac lymph in dogs, Ann Surg 175 299 1972
23 Malmberg P Time course of enzyme escape via heart lymph following myocardial infarction in the dog Scand J Clin Lab Invest 30 405 197
24 Feola M and Brockman S K Effect of steroids on cardiac lymph content of lysosomal enzyme acid phosphatase in experimental myocardial infarction Surg Forum 24 199 1973
25 Szabo G Magyer Z and Reffy A Lymphatic transport of enzymes after experimental myocardial infarction Lymphology 7 37 1974
26 Feola M and Glick G Cardiac lymph flow and composition in acute myocardial ischemia in dogs Am J Physiol. 229 44 1975
27 Uhley H N Leeds, S E and Elevitch F R Canine cardiac lymph potassium pH and flow after experimental myocardial infarction (39162) Proc Soc Exp Biol Med 151 146 1976
28 Taira A Matsuyama M Morishita Y., Terashi L., Kawashima Y Maruko M Arikawa K., Musata K., and Akita H Cardiac lymph and contractility of the heart Jap Circ J 40 665 1976
29 Fjeld N B Kluge T H Stokke K T and Skrede S The effect of generalized hypoxia upon flow and composition of cardiac lymph in the dog Europ J Clin Invest 6 255 1976
30 Feola M Cardiac lymph studies in acute myocardial ischemia in Pathophysiology and Therapeutics of Myocardial Ischemia edited by A M Lefer G J Kelliher and M J Rovetto Jamaica N Y 1977 Spectrum Publications p 337
31 Ali M Ellis A and Glick G Effects of methylprednisolone on cardiac lymph in acute myocardial ischemia in dogs Am J Physiol 232 H 602 1977
32 Takenaka F and Araki, H Effects of increased cardiac mechanical performances on flow rates of cardiac lymph in dogs Pflugers Archiv 370 31 1977
33 Comper W D and Laurent T C Physiologic function of connective tissue polysaccharides, Physiol. Rev 58 255 1978
34 Szabo G and Magyar S Effect of hyaluronidase on capillary permeability lymph flow and passage of dye-labelled protein from plasma to lymph Nature (Lond.) 128 3?7 1958

Table I Systemic hemodynamic parameters and blood gases*

		Unanesthetized control 37° C	Rewarming ether anesthesia			
			20° C	25 C	30° C	37° C
HR (beats/min)	NA	184 ± 8	56 ± 5	107 ± 7	139 ± 7	185 ± 12
	A	173 ± 3	60 ± 4	112 ± 6	163 ± 6†	193 ± 8
MAP (torr)	NA	120 ± 4	28 ± 1	48 ± 4	58 ± 3	65 ± 3
	A	133 ± 8	3[illegible] ± 3 †	75 ± 8 †	82 ± 6 ‡	[illegible]3 ± [illegible]
CO (mL/min /kg.)	NA	242 ± 36	63 ± 12	146 ± 23	179 ± 22	205 ± 19
	A	278 ± 46	86 ± 8	145 ± 18	223 ± 30	1[illegible]8 ± 38
SV (mL/kg)	NA	1.30 ± 0.17	1.15 ± 0.25	1.40 ± 0.25	1.31 ± 0.20	1.11 ± 0.0[illegible]
	A	1.62 ± 0.30	1.45 ± 0.11	1.36 ± 0.17	1.38 ± 0.20	0.9[illegible] ± 0.15
TVR (torr/ L/min.)	NA	85 ± 10	61 ± 8	50 ± 4	50 ± 4	[illegible]0 ± 5
	A	77 ± 5	50 ± 3	81 ± 8†	59 ± 4	67 ± 2†
pH	NA	7.48 ± 0.01	7.80 ± 0.08	7.64 ± 0.06	7.58 ± 0.04	7.40 ± 0.04
	A	7.51 ± 0.03	7.60 ± 0.08	7.57 ± 0.06	7.47 ± 0.08	7.32 ± 0.04
PaO (torr)	NA	113 ± 7	475 ± 28	409 ± 15	401 ± 20	371 ± 49
	A	105 ± 5	281 ± 79†	286 ± 78	228 ± 83	207 ± [illegible]9
PaCO (torr)	NA	31 ± 2	11 ± 1	12 ± 1	14 ± 2	[illegible]3 ± [illegible]
	A	33 ± 1	22 ± 4 †	22 ± 4†	25 ± 4†	36 ± 5†
Hematocrit (%)	NA	36 ± 3	25 ± 3	27 ± 3	28 ± 3	31 ± [illegible]
	A	37 ± 2	28 ± 1	32 ± 1	33 ± 3	30 ± 2

*The values are means and standard errors of the means from five non arrested (NA) and four arrested (A) monkeys. and † denote $p \leq 0.05$ and ‡ denote $p \leq 0.01$ and ‡ denote $p \leq 0.001$. The statistical significances are shown in asterisks ( ) when the results are compared to that of unanesthetized control values by paired t test. The statistical significances are shown in daggers (†) when the results are compared between NA and A values by Student s t test. HR = heart rate MAP = mean arterial pressure CO = cardiac output SV = stroke volum TVR = total vascular resistance

(MAP) was significantly below control throughout rewarming in both groups however the MAP of arrested animals was significantly greater than non arrested animals at 20° 25° and 30° C Cardiac output in both groups was 30% of control at 20 C In the non arrested animals cardiac output increased steadily with rewarming to values not significantly different from control at 37° C Arrested animals displayed a similar trend until 30 C at 37 C output decreased slightly and was significantly below control In both groups stroke volume was not significantly different from control except for a decrease in the arrested group at the completion of rewarming (37° C)

Total vascular and organ resistance (Table I Fig 1) Total vascular resistance (TVR) was insignificantly reduced when compared to the control value in the non arrested group at 20° C during rewarming A decline to a significant degree was noted at 25 C that was maintained through the completion of rewarming The TVR of arrested animals was significantly reduced at 20 C following resuscitation but resistance increased to near control at 25 C declined again significantly at 30° C and was rising at the completion of rewarming (37° C) When the two groups were compared arrested animals had significantly higher TVR at 25° and 37° C

Cerebral vascular resistance was slightly greater than control at 20° C in non arrested animals but declined steadily during rewarming and a significant reduction to 65% of control was noted at the completion of rewarming The cerebral vascular resistance of arrested animals was considerably less at 20 C than in non arrested counterparts (75% vs 120% of control values) although the difference was not significant due to individual variation During rewarming cerebral group vascular resistance in the arrested group increased with temperature until 30 C and decreased slightly thereafter

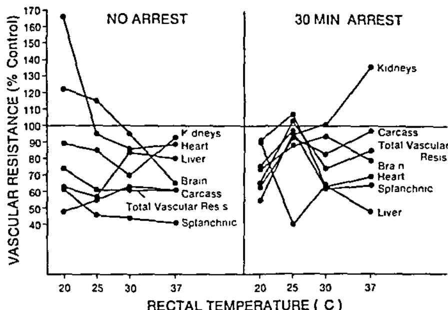


Fig 1 Total vascular and organ resistances plotted with the unanesthetized normothermic control value (not shown) as the 100% value

the body was ashed and a 20% aliquot of the mixed ash was also placed in vials for counting

Data collection and analysis Arterial central venous and left ventricular pressures and ECG (Lead II) were continuously recorded on a Hewlett/Packard model 7788A recorder with appropriate amplifiers Cardiac outputs were determined in duplicate by the dye dilution technique Immediately after each cardiac output determination and microsphere injection arterial blood samples were analyzed with a Radiometer Model 27 blood gas analyzer Temperatures of the pH and blood gas electrodes were preadjusted to sampling temperature in order to eliminate temperature correction errors [5]

The distribution of blood flow was determined by left ventricular injections of Sc ^{95}Nb ^{85}Sr Cr and ^{141}Ce nuclide labeled microspheres By using one isotope at each data collection point five separate blood flow determinations were done in each animal

The radioactivity of each vial containing tissue or ash was counted using a Packard NaI Model 9011 scintillation counter energy distribution patterns were recorded on a Packard Pulse Height analyzer and the composite spectra for all five nuclides were stored on magnetic tape for processing by a PDP 15 computer

The percentage of cardiac output (%Qt) to each organ was calculated as the amount of each nuclide's radioactivity in that organ divided by the total body count for that nuclide Blood flow to each organ was calculated as percentage of cardiac output times the cardiac output from the dye-dilution determination Peripheral and organ resistances were calculated by dividing the difference between mean arterial and mean venous pressure by flow

The raw data were tabulated and processed to yield the means and standard errors of means for each parameter Statistical significance was confirmed or denied where appropriate with the Student's t test for paired or unpaired data Changes were considered significant when the value for P was less than 0 05

Results

All animals were anesthetized and cooled uneventfully with changes in hemodynamic and blood gas parameters similar to those in the previously reported series were blood flow and distribution were studied during the cooling phase [24]

Hemodynamic parameters during rewarming Hemodynamic blood gas and hematocrit data are shown in Table I Heart rate which was about 30% of unanesthetized control values in both groups at 20° C was significantly less than control until the completion of rewarming in the non arrested animals. Mean arterial pressure

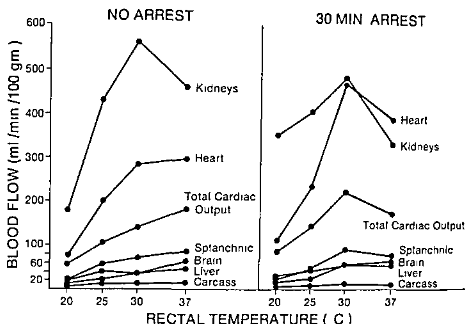


Fig 2 Absolute organ blood flows and total cardiac output during rewarming

resistance remained near 50% of control thereafter Arrested animals showed an increase to control value at 25° 30° and 37° C Arrested animals had significantly greater carcass vascular resistance from non arrested animals at 25° and 37° C

Distribution of cardiac output (Table II) In non arrested animals the %Qt distributed to the coronary circulation was decreased but insignificantly so, throughout rewarming Coronary %Qt was significantly decreased in the arrested group at 20° C but thereafter increased to levels significantly greater than in non arrested animals at the completion of rewarming (37° C)

The percentage of cardiac output distributed to the brain was significantly reduced (60% of control) at 20 C in animals not subjected to circulatory arrest Cerebral %Qt began to increase by 30° C and had returned to control at the completion of rewarming Animals subjected to arrest had a significantly greater %Qt distributed to the brain than non arrested animals at 20° and 25° C Furthermore %Qt was not significantly different from control at any time during rewarming in arrested animals

Renal %Qt was not significantly altered by rewarming in the non arrested group although absolute values tended to decrease between 30° and 37° C In the arrested group the trend was to a decreasing *renal %Qt which became significant*ly less than control value at the completion of rewarming

Hepatic %Qt tended to be greater than contr at 20° C with a decline to control by 37° C non arrested animals Arrested animals showe the opposite trend that is an initial decrease 20° C with a steady increase thereafter The trends although consistent were not statisticall significant

Splanchnic %Qt in non arrested anima increased during rewarming to significantly hig er levels at 30° and 37 C A similar trend wa observed in the arrested group

Carcass %Qt tended to decline in both group during rewarming but the differences were no significant

Changes in organ blood flow (Table II Fig 2) Coronary flow which was significantly belov control at 20° and 25° C increased with rewarm ing in the non arrested group Arrested animal tended to have greater coronary flows than non arrested animals and at 30 C the difference wa significant

Cerebral blood flow was significantly below control until rewarming was completed in th non arrested group Arrested animals showed sig nificantly reduced flow at 20 and 25° C but at 30° C the trend was toward control values at 37 C however flows had again decreased to levels significantly below control When the two groups were compared cerebral flow was twice as great *in arrested vs non arrested* animals at 20° C and at 25° C

Renal flows were subject to large individual

Table II Percentages of cardiac output (% Q) and absolute blood flows (mL/min /100 g tissue weight) to various organs and tissues*

		Unanesthetized control 37°C	Rewarming ether anesthesia			
			20° C	25 C	30° C	37° C
CO (mL/min)	NA	1419 ± 144	3̄70 ± 60	865 ± 112	1080 ± 143	1236 ± 103
	A	1633 ± 88	532 ± 66	907 ± 147	1322 ± 47	1041 ± 76
Heart (% Q)	NA	8 5 ± 1 6	4 8 ± 1 0	5.9 ± 1.2	6 9 ± 1.8	5 7 ± 0.2
	A	7.8 ± 0 5	5 6 ± 0 4	7.3 ± 1.2	9.2 ± 0 7	9 6 ± 1‡
mL/min./100g	NA	492 ± 101	77 ± 23	201 ± 26	284 ± 42	297 ± 28
	A	494 ± 70	113 ± 14	235 ± 61	469 ± 51†	388 ± 57
Brain (% Q)	NA	4 4 ± 0 4	2.8 ± 0 2	2 5 ± 0 4	2.9 ± 0 3	4 4 ± 0.3
	A	4.3 ± 0 3	4 3 ± 0.8†	4 6 ± 0 6†	3 8 ± 0 8	4.8 ± 0.5
mL/min./100g	NA	71 ± 10	12 ± 5	23 ± 3	35 ± 3	63 ± 8
	A	77 ± 5	26 ± 5	44 ± 5	56 ± 13	54 ± 4
Kidneys (% Q)	NA	18.5 ± 3 0	15 1 ± 1 5	14.2 ± 2 0	16.2 ± 2.2	11.3 ± 1 1
	A	13 6 ± 0 8	18.5 ± 2.9	14 0 ± 1 6	10 5 ± 1.9	8 8 ± 0.9
mL/min./100 g	NA	833 ± 155	177 ± 25	431 ± 134	562 ± 102	459 ± 70
	A	809 ± 82	352 ± 60 †	406 ± 41	482 ± 39	331 ± 25
Liver (% Q)	NA	6.3 ± 1 4	8 5 ± 1 3	7 0 ± 0 6	5.2 ± 1 1	6 8 ± 2.0
	A	7 4 ± 1 1	4 8 ± 1 0	4.8 ± 1 7	6.3 ± 2.8	8 7 ± 2.4
mL/min./100 g.	NA	58 ± 17	20 ± 5	39 ± 7	36 ± 8	50 ± 12
	A	83 ± 18	17 ± 4	24 ± 9	57 ± 19	62 ± 16
Splanchnic (% Q)	NA	23 1 ± 1 4	26 8 ± 4 2	29.9 ± 3 4	30 6 ± 3 0	31 7 ± 2 1
	A	23.2 ± 1.9	19.9 ± 2 6	25 1 ± 4 1	29 8 ± 5.2	31.8 ± 3 4
mL/min./100 g	NA	71 ± 16	21 ± 3	56 ± 9	71 ± 11	87 ± 14
	A	89 ± 16	24 ± 4	47 ± 13	91 ± 17	77 ± 11
Carcass (% Q)	NA	45.5 ± 2 8	50 1 ± 2 1	47 1 ± 3 7	43 1 ± 3.5	46 1 ± 1.3
	A	49.9 ± 2 6	51 0 ± 4.8	48 0 ± 2.5	45 5 ± 5 4	43 6 ± 4.1
mL/min./100 g	NA	19 ± 4	6 ± 2	12 ± 3	13 ± 3	16 ± 2
	A	17 ± 4	5 ± 1	8 ± 1	13 ± 3	10 ± 3

*The symbols for statistical analyses are described in Table I

Coronary vascular resistance in the non arrested group was at about 150% of control at 20 C during rewarming decreased rapidly to slightly below control at 25 C and decreased only slightly thereafter These changes were not statistically significant due to large individual variation In the arrested group coronary resistance was similar to control value at 20 C but was significantly reduced at 30° and 37° C

Renal vascular resistance was not significantly changed from preanesthetic control throughout rewarming in the non arrested group Arrested animals had significantly decreased renal vascular resistance at 20° C but resistance increased during rewarming to levels significantly greater than in non arrested counterparts of the completion of rewarming

Splanchnic vascular resistance was the most variable of the organ systems evaluated In both groups hepatic resistance was below control throughout rewarming

Carcass vascular resistance in the non arrested group was reduced at 20° C during rewarming The reduction was significant at 25° C and

ry reduction in flow to other organs and a previous study in dogs showed no change in blood volume at the onset of rewarming.[5] Thus it seems unlikely that the effects of surface rewarming on TVR and carcass vascular resistance at 20° C can be accounted for by major changes involving vasomotion.

The TVR in non arrested animals was similar at 25°, 30°, and 37° C during rewarming and was significantly less than the unanesthetized normothermic control value. While the influence of surface heating described above may explain generally lower resistances during rewarming than at comparable temperatures during cooling, it also suggests that TVR should change progressively with rewarming instead of remaining stable at and after 25° C. We have examined other factors that are capable of influencing TVR during rewarming. These include (1) oxygen consumption, which has been shown to be higher at comparable temperatures during rewarming[15] (2) anesthetic level, which, as judged by clinical signs is the sum of the effects of anesthetic concentration and cold depression (circulatory arrest may also exert a depressive effect since arrested animals usually require less anesthetic during rewarming) (3) cardiac output, which progressively rises during rewarming but was greater at 20° C and less at 37° C in arrested vs non arrested animals (4) blood volume, which is unchanged following rewarming in non arrested dogs but decreased in animals subjected to arrest[8] (5) plasma catecholamines, which are markedly elevated for a brief period following circulatory arrest at 20° C but are unchanged in non arrested dogs.[16] While the interaction of these factors is not entirely understood, it is clear that TVR differences during rewarming vs cooling and between the arrested and non arrested groups in this study involve varying degrees of functional autoregulation at deep hypothermic levels.

Blood flow in individual organs. Assessing the adequacy of blood flow to the brain is difficult since it shows little correlation with functional and histopathological changes.[17, 22] In addition the level of cerebral blood flow necessary to maintain basal c nditions may be considerably below the level necessary to provide maximal tissue reserves and e the maximum possible safe circulatory o n time at a given temperature. Recent stud Ohmura and associates[18] and by Hagerdal and colleagues[5, 6] give credence to the concept that the integrity of the brain can probably only be accurately monitored on the metabolic or biochemical level. Until better monitoring methods are established, however, an interim approach involves comparing cooling and rewarming cerebral flows in arrested and non arrested animals. Using our technique of deep hypothermia,[13] we have maintained surface cooled dogs at temperatures below 20° C for up to two hours following surface rewarming; no change—including such judgmental factors such as appetite, degree of activity, etc.—could be detected. Half term puppies cooled in utero and not arrested in mothers who were arrested for one hour have come to normal delivery,[12] grown to adulthood and been cooled again and arrested for one hour and have not suffered detectable changes (unpublished data). These observations and other studies of cerebral oxygen consumption and metabolism[5, 18] leave little doubt that cerebral blood flow during cooling is adequate with the method described herein.

During rewarming absolute cerebral blood flow was always greater than at equivalent cooling temperatures. Furthermore, the cerebral %Qt, absolute flow, and cerebral vascular resistance data confirm a reactive hyperemia following resuscitation and rewarming in arrested animals that did not occur in non arrested animals.

In both groups of animals during rewarming, coronary blood flow was consistently maintained at higher values than at comparable temperatures during cooling. These flows occurred despite differences in cardiac output and coronary vascular resistance, strongly suggesting intact autoregulative function. Under normothermic basal conditions coronary venous oxygen content is very low so that an increased oxygen demand must be supplied by an increase of coronary blood flow. Similarly, coronary blood flow must increase to compensate for decreased oxygen supply due to reduced oxygen content or other causes such as a shift in the oxyhemoglobin dissociation curve. During hypothermia the interaction of these factors may be complex; however, the fact that myocardial oxygen requirement is determined by the amount and kind of cardiac work has yet to be disproven under conditions of hypothermia. At normothermia, cardiac indices have been developed which relate cardiac work to oxygen consumption and hence to coronary flow. Such rela

variations in both groups It was apparent however that renal flow in both groups increased during rewarming from 20 to 30° C and then decreased with further warming to 37° C Furthermore arrested animals had significantly greater flows at 20° C than did non arrested animals

Hepatic arterial flow in the non arrested group was approximately 30% of control at 20° C and increased with temperature to near control by 37° C These changes were not statistically significant due to individual variations during the pre anesthetic control determinations Arrested animals had significantly reduced hepatic flows at 20 and at 25° C with an increase toward control by 37 C

Splanchnic blood flow increased throughout rewarming in both groups and was significantly greater than control in non arrested animals at 30 and at 37° C

Carcass flows in both groups were significantly reduced from control values at 20 C At 37° C carcass flow in arrested animals was still significantly reduced whereas it had returned to control in non arrested animals

Discussion

Our previous report[2] discussed the effects of surface cooling and ether anesthesia on regional blood flow It was also noted that only about five separate microsphere injections are practical on this basis we elected to study the cooling and rewarming phrases of deep surface hypothermia separately While this approach comprises statistical comparisons between the cooling and rewarming phases it has the advantage of doubling the number of observations over the whole procedure

The present study reveals that rewarming is a complex process with vascular resistance output fraction to various organs and organ blood flow varying in response to both rewarming and circulatory arrest At 20° C shortly after the initiation of surface rewarming the TVR in both arrested and non arrested animals decreased abruptly to approximately 50% of the levels seen at 20° C during cooling As rewarming continued the TVR of non arrested animals stabilized at levels significantly below the awake control whereas arrested animals showed fluctuating generally higher TVR (Table I) Since cardiac output is only slightly (and insignificantly) greater in the arrested group at 20° C it seems likely that rewarming *per se* exerts the dominant influence during the first few minutes of surface rewarming In dogs cooled by ice-water immersion subcutaneous temperatures quickly fall to 10 C or less and skeletal (thigh) muscle also cools rapidly the latter usually reaching 15° C while the core (brain liver rectal) temperature is at 20 C (unpublished data) During rewarming in a 40 C bath skin and skeletal muscle temperatures are normothermic or nearly so by the time core temperature has reached 25° C The fact that whole body vascular resistance and carcass vascualr resistance change in a parallel fashion at the initiation of rewarming again strongly suggests the dominant role of surface heating as a cause of the abrupt reduction of TVR

There is considerable evidence that the above changes with the induction of surface rewarming are not entirely the direct vasodilatative effect of heat Several studies have shown that both cooling[1] [?] and ether anesthesia can result in maximal peripheral capillary and arteriolar dilatation in which case significant cutaneous or skeletal muscular vascular dilatation should not occur with the induction of surface rewarming Furthermore the relationships between temperature and blood viscosity have been well documented [9] and it has been observed that blood viscosity rises rapidly with a decrease in temperature below 27° C [9] [3] As surface cooling is started skin temperature decreases rapidly to near 0° C while the core is still normothermic creating a temperature and temperature-induced viscosity gradient in the central vs the peripheral vascular compartment Surface rewarming quickly reverses this gradient thus the immediate decrease in skin and skeletal muscle vascular resistance noted in this study at the onset of surface rewarming may be the result of reducing blood viscosity in the vessels closest to the surface This effect would potentially improve venous return to the heart and tend to explain (1) why cardiac output is greater at 20° C during rewarming than at 20° C during cooling and (2) why cardiac output begins to increase during surface rewarming before a detectable increase in core temperature is evident

Carcass vascular resistance is halved by the initiation of surface rewarming at 20° C If this is the result of vascular dilatation then intravascular volume would increase accordingly or be compensated for by a decrease in the volume (vasoconstriction) in other organ systems The current study shows that there is no compensato

ng rewarming especially in arrested animals CO ippeared to be similar to those noted at compar ible cooling temperatures until 30° C during 'ewarming thereafter CO did not fully recover to iwake control levels These data suggest that 'egional flow is redistributed from the carcass and 'enal circulations to cerebral and coronary circu ations in response to hemodynamic alterations luring surface rewarming It was concluded that iutoregulative responses to both circulatory irrest and hemodynamic factors are elicited dur ng surface rewarming from deep hypothermia to !0° C with the method described

We would like to thank Mr Clifford Pitts and Mr Lewis 'urcell for their excellent assistance

IEFERENCES

1 Covino B G., and Beavers W R Hind limb body flow during immersion hypothermia J Appl. Physiol. 10 146 1967
2 Dillard D H Mohri H., Hessel, E A II Anderson H N Nelson R J Crawford, E W Morgan B C Winterscheid L C and Merendino K A Correction of total anomalous pulmonary venous drainage in infants utilizing deep hypothermia with total circulatory arrest Circulation 35(Suppl. I) 105 1967
3 Dillard D H Mohri, H Merendino K A Morgan B C Baum D., and Crawford E W Total surgical correction of transposition of the great arteries in chil dren less than six months of age Surg Gynecol Obstet 129 1258 1969
4 Dillard D H Mohri, H and Merendino K A Correc tion of heart disease in infancy utilizing deep hypother mia and total circulatory arrest J Thorac Cardiovasc Surg 61 64 1971
5 Hagerdal M., Harp J and Siesjo B K Effect of hypothermia upon organic phosphates glycolytic metab olites citric acid cycle intermediates and associated amino acids in rat cerebral cortex, J Neurochem 24 743 1975
6 Hagerdal M Welsh F A Keykhah M M Perez, E and Harp J R Protective effects of combinations of hypothermia and barbiturates in cerebral hypoxia in the rat Anesthesiology 49 165 1978
7 Hershey S G Zweifach, B W and Rovenstine E A Effects of depth of anesthesia on behavior of peripheral vascular bed, Anesthesiology 14 245 19s3
8 Hessel E A. II and Dillard D H Blood volume and albumen kinetics during deep surface hypothermia Surg Gynecol Obstet (In press)
9 Hessel, E A Schmer G and Dillard D H Platelet kinetics during deep surface hypothermia J Surg Res 28 23 1980
10 Kawashima Y Okada K Kosugi, I In Nami H Yamaguchi, Y Fujihara T and Yamamura H Changes in di tribution of cardiac output by surface induced deep hypothermia in dogs J Appl Physiol 40 876 1976
11 Manhas D R Wong K C Mohri H., Sands, M P., and Merendino K A Effects of surface induced deep hypo thermia diethyl ether anesthesia and respiratory alkalo sis on myocardial metabolism following total circul ory arrest in dogs Anesth Analg 53 77? 1974
12 Mohri, H Barnes R W Winterscheid L C Dillard, D H and Merendino K A Challenge of prolonged su pended animation A new method of surface induced deep hypothermia Ann Surg 168 779 1968
13 Mohri H Dillard D H Crawford E W Martin, R E and Merendino K A Method of surface-induced deep hypothermia for open heart surgery in infants, J Thorac Cardiovasc Surg 58 26? 1969
14 Mohri H Hessel E A. II Nelson R J Matano I, Anderson H N Dillard D H and Merendino K A. The use of Rheomacrodex and controlled hyperventila tion in prolonged circulatory arrest under deep hypother mia induced by surface cooling A method for open hea surgery in infants Am J Surg 112 241 1966.
15 Mohri H Martin W E Sato S Sands, M P Dillard, D H and Merendino K A Oxygen utilization during *surface induced deep hypothermia* Ann Thorac Surg 18 494 1974
16 Mohri H Pitts C L Sands M P., Manhas, D R, Dillard D H and Merendino K A. Effects of surface-induced hypothermia and circulatory occlusion on pla ma catecholamines Surgery 72 596 19 ?
17 Montgomery L D and Williams, B A Variation of forearm hand and finger blood flow indices with ambient temperature Aviat Space Environ Med 48 231 19–
18 Ohmura A Wong K C Lu T Ruttenburg H and Chang R Deep hypothermia and circulatory arrest Effect on cerebrospinal fluid electrolytes in newborn lambs Cryobiology 15 19? 1978
19 Rand P W Lacombe E Hunt H E and Austin W H Viscosity of normal human blood under normother mic and hypothermic conditions J Appl. Physiol 19 117 1964
20 Rittenhouse E A Mohri H Reichenbach D D and Merendino K A Morphologic alterations in vital organs after prolonged cardiac arrest at low body temper ature Ann Thorac Surg 13 564 1972
21 Rittenhouse E A Ito D S Mohri H and Merendino K A Circulatory dynamics during surface-induced deep hypothermia and after cardiac arrest for one hour J Thorac Cardiovasc Surg 61 359 1971
22 Rudy L W Boucher J K., and Edmunds L H The effect of deep hypothermia and circulatory arrest on the distribution of systemic blood flow in rhesus monkeys J Thorac Cardiovasc Surg 64 706 1972
23 Sands M P., Mohri H Sato S Mannik M Hessel E A. II and Dillard D H Hematorheology during deep hypothermia Cryobiology 16 ?29 1979
24 Su J Y Amory D W., Sands M P., and Mohri, H Effects of ether anesthesia and surface induced hypo thermia on regional blood flow AM HEART J 97 5? 1979
25 Tempel G E Musacchia X J and Jones, S B. Mechanisms responsible for decreased glomerular filtra tion in hibernation and hypothermia J Appl Physiol 42 420 1977
26 Zarins C K and Skinner D B Hemodynamics and blood flow distribution following prolonged circulatory a at 5 C., Am J Physiol 229 275 1975

tionships have not been well established during hypothermia so that changes in coronary flow with various cooling methods have resulted in much conjecture Studies by others have shown that coronary flow and coronary resistance may increase or decrease depending upon temperature and the method of cooling [6, 2, 26] We suggest however that there is no reason to believe that the principles of normothermic coronary autoregulation (primarily oxygen demand) do not function within the temperature range than can be achieved with surface cooling (18° to 20 C) It also seems likely that a better understanding of the determinants of myocardial oxygen demand during hypothermia would resolve many of the apparent discrepancies regarding coronary flow reported in the literature

The present study revealed coronary vascular resistance and flow patterns consistent with a hyperemic response following circulatory arrest that was not evident in non arrested animals In previous studies using dogs under similar conditions we found that plasma catecholamines are elevated immediately following circulatory arrest[1] and that coronary A V lactate balance became negative These data support the conclusion that the coronary circulation does respond to metabolic stimuli even at 20° C

Our data suggested that renal blood flow during cooling paralleled the decline in cardiac output since the renal %Qt was unchanged During rewarming the significantly greater absolute renal flow in arrested animals at 20 C as compared to immediately rewarmed animals probably represents a hyperemia As rewarming progressed the renal %Qt decreased especially in arrested animals so that absolute flow was below control values at 37° C The cause of these reduced flows is explained by the slightly reduced cardiac output[15, 7] and blood and plasma volumes that are known to occur following rewarming with this hypothermia method The absence of primary post rewarming renal failure and histopathologic changes in dogs subjected to a similar protocol is consistent with the hypothesis that the transient shift of flow away from the kidneys is related to cardiovascular dynamics and blood volume rather than to low temperature *per se* In fact Tempel and associates [5] have shown that changes in these parameters are sufficient to explain decreased renal function at low temperatures during both induced hypothermia and normal hibernation

From a practical clinical standpoint such considerations imply that the cardiovascular and/or blood volume status rather than primary kidney alterations should be suspected as the cause of renal malfunction in the post hypothermic patient with poor urine output Additional studies should be done to confirm and expand these relationships and their validity in the patient with congenital cardiac disease following repair under deep hypothermia

Interpretation of liver and splanchnic flow data was hampered by large individual variations While in part related to methodology the greater variance in these systems might be expected because they play a major role in terms of immediate circulating volume adjustments Morphologic studies in dogs revealed some dilatation of hepatic sinusoids after cooling to 18 C [6] and we have recently shown that the hepatic sinusoids are the site of the platelet sequestration phenomenon associated with surface cooling [9]

This study demonstrates that the regional distribution of blood flow is not necessarily similar at specific temperatures depending (1) upon the stage of the procedure (cooling as opposed to rewarming) and (2) upon the addition of a period of circulatory arrest prior to rewarming This knowledge and the microsphere technology if expanded will likely provide a basis for comparing hypothermia techniques especially if low temepratury regional flow requirements can be ascertained and correlated to functional and histopathologic changes following rewarming

Summary

Regional blood flow and distribution of cardiac output (CO) were evaluated by the radioactive microsphere technique in rhesus monkeys during surface rewarming following the induction of deep hypothermia (20° C) under deep ether anesthesia A comparison of animals subjected to 30 minutes of circulatory arrest and those not arrested revealed cerebral coronary and renal vascular resistance and flow patterns consistent with a hyperemic response to circulatory arrest at 20° C Throughout rewarming cerebral and coronary absolute flows tended to be at or above the flows noted at comparable cooling temperatures in a previous study Renal flow fraction (% Qt) were well preserved during rewarming to 30° C but a decrease was observed thereafter Carcass (muscle skin bone) %Qt was also reduced follow

Table I Serum and CSF quinidine concentrations in eight human subjects

Subject	Age/sex	*Serum quinidine total (μg/ml)*	*Percent unbound*	*Serum quinidine unbound (μg/ml)*	*CSF quinidine (μg/ml)*	*Ratio of CSF to unbound serum concentrations*
1	31/M	2 27	13 1%	0 30	0 013	0 04
2	24/M	1.25	18 1%	0 23	0 039	0 17
3	41/M	2 96	21 3%	0 64	0 071	0 11
4	70/M	1 98	22 2%	0 44	0 079	0 18
5	29/F	0 91	13 2%	0 12	0 011	0 09
6	49/M	2 14	17 4%	0 37	0 053	0 14
7	38/F	0 74	18 2%	0 13	0 048	0 37
8	23/M	1 78	16 7%	0.30	0 054	0 18
Mean (± SE)		1 75 (± 0 26)	17 5% (± 1 2%)	0 32 (± 0 06)	0 046 (± 0 009)	0 16 (± 0 03)

Table II Relation of unbound serum quinidine to total serum and CSF concentrations in four dogs

	Animal number			
	1	*6*	*7*	*8*
Mean percent unbound quinidine (range)	18 8% (15 0 25 5)	7 9% (5 5 12 5)	14 8% (11 0 24 6)	15 6% (9 4 26 6)
Correlation coefficient for unbound vs total serum quinidine	0 67	0 44	0 76	0 63*
Mean ratio of CSF to unbound serum quinidine	0 45	0 37	0 46	0 46
Correlation coefficient for CSF vs unbound serum quinidine	0 89*	0 81	0 8?	0 64

= p < 01 = p < 05

of quinidine base was injected intravenously over a period of one minute Samples of blood (4 to 5 ml) and CSF (1 to 2 ml) were simultaneously taken before the infusion and at the following post infusion times 5 10 15 30 and 45 minutes 1 1 5 2 2 5 3 3 5 and 4 hours then hourly for up to 8 hours after the dose Serum and CSF were stored at –20° C until the time of assay

After an interval of two weeks serum quinidine kinetics were studied again without anesthesia in two of the four dogs to assess the effect of the anesthetic procedure CSF was not sampled

In vitro study The partitioning of quinidine between wat r and n octanol at physiologic pH was determi d in vitro A solution of quinidine sulfate (5 μg [illegible]) in phosphate buffer (pH 7 4) was shaken w [illegible] equal volume of octanol The quinidine conc [illegible] ion in the aqueous phase was determined be [illegible] d after the octanol extraction

Analysis of sa [illegible] s Quinidine concentrations in all samples (se [illegible] CSF or phosphate buffer) were determined by modification of the double extraction spectrophotofluorometric technique The extent of quinidine protein binding in each serum sample was determined by equilibrium dialysis [9]

Results

Percent unbound quinidine in serum among the eight human subjects ranged from 13 1 to 22 2% (Table I) CSF concentrations were always lower than unbound serum levels at the time of sampling The mean (± SE) CSF to unbound serum concentration ratio was 0 16 (±0 03) with a range of 0 04 to 0 37

The mean percent unbound serum quinidine among the four dogs ranged form 7 9 to 18 8% (Table II) However percent unbound serum quinidine increased with increasing total quinidine concentrations (Table II Fig 1) consistent with concentration dependent protein binding

Quinidine appeared promptly in CSF of all four dogs (Fig 2) Quinidine concentrations in serum

Entry of quinidine into cerebrospinal fluid

Hermann R Ochs M D
David J Greenblatt M D
Brian L. Lloyd M B B S F R A C P*
Elaine Woo M D**
M Sonntag M D
Thomas W Smith M D
Bonn W Germany and Boston Mass

Central nervous system (CNS) toxicity is commonly associated with the use of quinidine derivatives in clinical practice [1-4] The characteristic syndrome of mild cinchonism includes headache tinnitus and blurring of vision More severe cinchonism can include marked auditory and visual disturbances as well as behavioral and neurologic disorders [5,6] Gastrointestinal toxicity attributable to quinidine (diarrhea nausea vomiting) may also refect effects on the CNS inasmuch as these symptoms can be caused by parenteral administration of quinidine [7] Furthermore quinidine can produce emetic movements in eviscerated animals [8]

Despite the clinical importance of quinidine s central toxicity few data are available on the rate and extent of its entry into the CNS The present study assessed simultaneous serum and cerebrospinal fluid concentrations of quinidine in a series of human subjects We also studied the rate and extent of quinidine entry into cerebrospinal fluid in dogs

Methods

Human studies Eight volunteers scheduled for diagnostic lumbar puncture participated after giving informed consent Subjects received 500 mg of quinidine bisulfate at 12 hours and again at 2 hours prior to the procedure A sample of venous blood together with a 1 to 2 ml aliquot of cerebrospinal fluid (CSF) were obtained simultaneously Blood samples were allowed to clot at room temperature then were centrifuged Serum and CSF were stored at −20 C until the time of assay

Animal studies Four adult mongrel dogs (20 to 32 kilograms) were anesthetized with intravenous pentobarbital (30 mg /kg) intubated and ventilated with a Harvard respirator to maintain arterial oxygen tension within normal limits Body temperature was maintained with a heating pad and fluid losses were approximately replaced with intravenous 0.9% sodium chloride solution A 7 5 cm spinal needle (19 gauge) was inserted into the cisternum magnum to allow repeated sampling of CSF

Quinidine gluconate † equivalent to 10 mg /kg

From the Medizinisch Universitatsklinik, Bonn W Germany Th Division f Clinical Pharmacology Tufts-New E gland Medical Center The Clinical Pharmacology Unit Massachusetts General Hosp tal, Boston and the C rdiovascular Division Departm nt of Medicine, P t r Bent Brigham Hospital, Boston

Supported in part by Grants MH 12279 (Dr Greenblatt) and HL-18003 (Dr Smith) from the United St tes Publi He lth Serv e Dr O hs was supported by Deutsche Forsch ngsg meinschaft, Bonn Bad Godesberg West Germany Dr Lloyd was an Ov rseas Fellow of the Nation l H art Foundation of Australia Dr Woo was the recip ent of a research fellowship (No HL-05723) from the U ited States Public H alth Service

This w rk was done in part during the tenure of the foll wing rese ch gr t i aid awards (to D Greenblatt) No 13-006- 06 from the American Heart Associat n Western M ssachusetts Division and the American Heart Assoc ation M ssa husetts Affiliate Inc- and N 13 1 767 from the American Heart Association, Central Massachusetts Divisi n.

Rec i ed f r publicat n Apr 9 19 9

Accepted f r publi ation July 6 1979

Reprint req ests Dr D id J Greenblatt Bo 1007 Di isi n of Clinic l Pharma ology Tufts New E gland Medic l Ce te 171 H r rison A e Boston Mass. 02111

*Present ddress Royal P rth Hosp t l, Perth, W Austr lia

**Prese t address Massa husetts Rehabilitatio Hospital Boston.

*Chinidin Durules, Ast a Chemicals, Wed l/Holst in W Germany Contains 77% quinidin base by weight.

†Eli Lilly nd Co Indi napolis Indiana USA

0002-8703/80/090341 + 06$00 60/0 © 1980 The C V Mosby Co

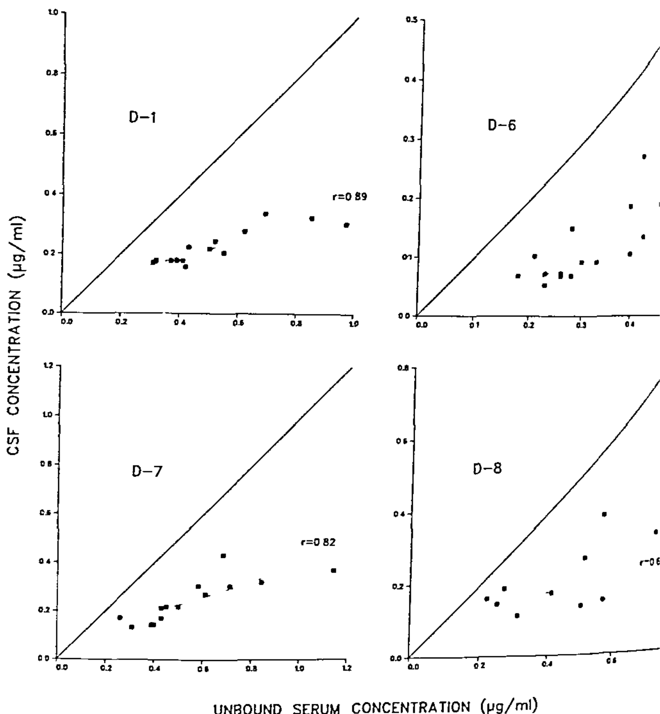


Fig 3 Simultaneous unbound serum and CSF concentrations of quinidine in four animals *Solid diagnonal lines* are the theoretical functions of identity (unbound serum = CSF concentration) Actual data points always fall below the line (unbound serum greater than CSF concentration) *Dashed lines* were determined by least-squares regression analysis.

CSF concentrations were considerably lower than unbound serum concentrations in each of the human subje t studied The findings were con firmed when the rate and extent of quinidine entry into (SF was studied in dogs The results of the animal dies are not likely to reflect non equilibrium ditions due to slow entry of quin idine into CSF In fact quinidine appeared ve rapidly in dog CSF following which CSF a unbound serum concentrations declined in para lel with a nearly constant ratio maintai between the two This strongly suggests th distribution equilibrium was rapidly attained In the human studies, the clinical con trai

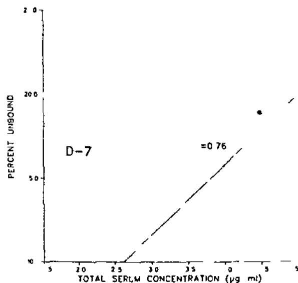


Fig 1 Relation of the extent of quinidine protein binding to total serum quinidine concentration in Dog No 7 Note that binding decreases with increasing total serum concentration (r = 0 6 p < 0 01)

(unbound and total) and in CSF declined in parallel CSF quinidine concentrations were always less than unbound serum levels (Figs 2 and 3) although the two were highly correlated in all four animals The mean ratio of CSF to unbound serum quinidine ranged from 0 37 to 0 45 among the four dogs (Table II)

The elimination half life of quinidine in the two animals studied both without and with barbiturate anesthesia was prolonged by anesthesia from 3 7 to 16.2 hours and from 5.3 to 12 3 hours respectively (Fig 4) Total quinidine clearance was correspondingly reduced during anesthesia The findings suggest that some aspect of the general anesthetic procedure is associated with marked impairment of quinidine clearance

The ratio of quinidine concentrations measured in the aqueous phase before and after mixing with octanol was 133 indicating greater than 99% partitioning into octanol at physiologic pH

Discussion

Physicochemical factors influencing the passage of drugs and plasma constituents from blood to CSF are known to include the degree of drug binding to plasma protein the degree of ionization at physiologic pH and the lipophilicity of the undissociated molecule Many drugs are moderately lipophilic when undissociated and at physiologic pH are at least partly undissociated

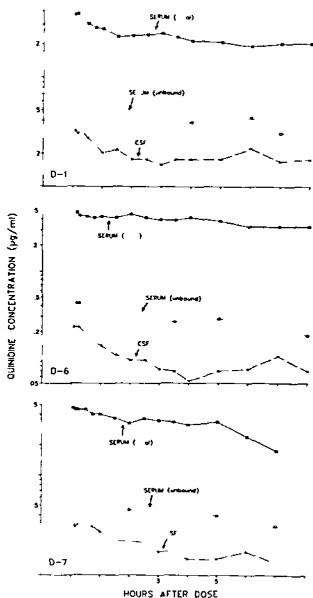


Fig 2 Concentrations of quinidine in serum (unbound and total) and in CSF following intravenous quinidine (10 mg /kg of quinidine base) administered at time zero to three representative dogs

If the passage of such compounds into CSF occurs by passive diffusion then CSF concentrations after attainment of distribution equilibrium are approximately equal to the unbound concentration in plasma[15] In the case of quinidine a weak organic base its octanol water partition characteristics suggest that the fraction of total drug existing as the lipophilic free base at physiologic pH is sufficient to favor rapid equilibration of unbound serum quinidine with CSF if passive diffusion alone governed the process[17] However

Effects in Hospitalized Patients Experiences of the Boston Collaborative Drug Surveillance Program 1966-1975 edited by R R Miller and D J Greenblatt New York, 1976 John Wiley & Sons Inc pp 43 54
4 Cohen I S Jick H and Cohen S I Adverse reactions to quinidine in hospitalized patients findings based on data from the Boston Collaborative Drug Surveillance Program Progr Cardiovasc Dis 20 151 1977
5 Gilbert G J Quinidine dementia J A M.A 237 2093 1977
6 Kerr F Kenoyer G and Bilitch, M Quinidine over dose neurological and cardiovascular toxicity in a normal person Br Heart J 33 629 1971
7 Greenblatt D J Pfeifer H J Ochs, H R Franke K MacLaughlin D S Smith T W and Koch Weser J Pharmacokinetics of quinidine in humans after intravenous intramuscular and oral administration J Pharmacol Exp Ther 202 365 1977
8 Ernestene A and Louis S The mechanism of vomiting induced by quinidine II J Pharmacol Exp Ther 48 359 1933
9 Woo E and Greenblatt D J Pharmacokinetic and clinical implications of quinidine protein binding J Pharm Sci. (In press)
10 Rall D P Stabenau J R., and Zubrod C G Distribution between blood and cerebrospinal fluid general methodology and effect of pH gradients J Pharmacol Exp Ther 125 185 1959
11 Rall, D P., Moore E Taylor N and Zubrod C G The blood-cerebrospinal fluid barrier in man Arch. Neurol 4 318 1961
12 Brodie B B Kurz H and Schanker L S The *importance of dissociation constant and lipid solubility* in influencing the passage of drugs into the cerebro pinal fluid J Pharmacol Exp Ther 130 20 1960
13 Mayer S Maickel R P and Brodie B B Kinetics of penetration of drugs and other foreign compounds into cerebrospinal fluid and brain J Pharmacol. Exp Ther 127 205 1959
14 Oldendorf W H Lipid solubility and drug penetration of the blood brain barrier Proc Soc Exp Biol. Med 147 813 1974
15 Oldendorf W H. Hyman S Braun L and Oldendorf S Z. Blood brain barrier penetration of morphine codeine heroin, and methadone after carotid injection Science 178 984 1972
16 Oldendorf W H Blood brain barrier permeability to drugs Ann Rev Pharmacol 14 239 1974
17 Rapoport S I Blood Brain Barrier in Physiology and Medicine New York, 1976 Raven Press
18 Troupin A S and Friel P Anticonvulsant level in saliva serum and cerebrospinal fluid Epilepsia 16 223 1975
19 Jalling B Plasma and cerebrospinal fluid concentrations of phenobarbital in infants given single doses Dev Med. Child Neurol. 16 781 1974
20 Schmidt D and Kupferberg, H J Diphenylhydantoin phenobarbital and primidone in saliva plasma, and cerebrospinal fluid Epilepsia 16 735 1975
21 Johannessen S I and Strandjord R.E Concentration of carbamazepine (Tegretol) in serum and in cerebrospinal fluid in patients with epilepsy Epilepsia 14 [illegible] 1973
22 Agurell S Boreus L O Gordon E Lindgren, J E. Ehrnebo M and Lonroth, U Plasma and cerebrospinal fluid concentrations of pentazocine in patients assay by mass fragmentography J Pharm. Pharmacol 26 1, 1974
23 Christensen J M and Holfort S Methaqualone in human serum and cerebrospinal fluid after oral intake J Pharm Pharmacol 27 538 1975
24 Lund L. Berlin A and Lunde P K M Plasma protein binding of diphenylhydantoin in patients with epilepsy Clin Pharmacol Ther 13 196 1972
25 Muscettola G., Goodwin F K. Potter W Z. Claeys M. M., and Markey S P Imipramine and desipramine in plasma and spinal fluid Arch. Gen Psychiatry 35 621 1978
26 Kanto J., Kangas L. and Siirtola T Cerebrospinal fluid concentrations of diazepam and its metabolites in man Acta Pharmacol. Toxicol. 36 328 1975
27 Stanski D R Greenblatt D J Selwyn A Shader R. I. Franke K and Koch Weser J Plasma and cerebrospinal fluid concentrations of chlordiazepoxide and its metabolites in surgical patients, Clin Pharmacol. Ther 20 547 1976
28 Gibaldi, M., and Perrier D Pharmacokinetics, New York, 1975 Marcel Dekker Inc
29 DiChiro G Hammock, M K and Bleyer W A. Spinal descent of cerebrospinal fluid in man Neurology 26 1, 1976
30 Lorenzo A V and Spector R The distribution of drugs in the central nervous system, *in* Transport Phenomena in the Nervous System edited by G Levi, L. Battistin and A. Lajtha New York 1976 Plenum Publishing Corp pp 447-461
31 Spector R The transport of gentamicin in the choroid plexus and cerebrospinal fluid J Pharmacol. Exp Ther 194 82 1975
32 Wang J H and Takemori A E Studies on the transport of morphine out of the perfused cerebral ventricles of rabbits J Pharmacol Exp Ther 181 46 1972
33 Ashgar K., and Way E L. Active removal of morphine from the cerebral ventricles J Pharmacol Exp Ther 175 75 1970
34 Vatner S F., and Braunwald E Cardiovascular control mechanisms in the conscious state N Engl. J Med 293 970 1975

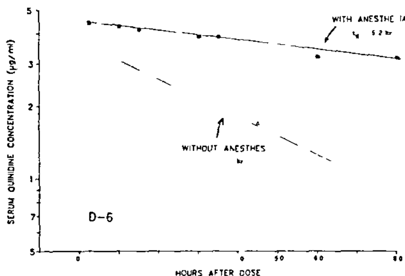


Fig 4 Total serum quinidine concentrations in Dog No 6 after intravenous injection of quinidine (10 mg/kg of quinidine base) on two occasions, with and without concurrent general anesthesia The elimination half life ($t_{½}$) was more than four times longer when quinidine was given during general anesthesia

requiring lumbar CSF sampling might lead to lower CSF quinidine concentrations than those present at sampling sites closer to the brain due to the time required for circulation of CSF [9] However this is unlikely to account for the large differences between unbound serum and CSF quinidine concentrations The findings therefore suggest that passage of quinidine into CSF is not determined simply by passive diffusion It may be that quinidine participates in an active transport such as that known to remove from CSF other basic substances including morphine codeine atropine and gentamicin [33]

Total quinidine clearance in the dog studies was markedly lower in the anesthetized state when compared to values measured upon retesting in the unanesthetized condition This could be explained either by a direct inhibitory effect of pentobarbital upon hepatic biotransformation of quinidine or by hemodynamic changes associated with the anesthetized condition In any case it is clear that kinetic properties of drugs established in studies of conscious animals or humans are not necessarily applicable during general anesthesia

Summary

Some of the unwanted effects of quinidine commonly occurring in clinical practice involve the central nervous system We therefore assessed the rate and extent of quinidine passage into cerebrospinal fluid (CSF) in humans and dogs In eight human subjects receiving oral quinidine therapy lumbar CSF quinidine concentrations averaged 16% of unbound serum concentrations (range 4% to 37%) The findings were confirmed when simultaneous serum (total and unbound) and CSF quinidine concentrations were followed for up to 8 hours after a single intravenous dose of quinidine in anesthetized dogs Quinidine appeared promptly in CSF of all animals, but CSF concentrations averaged only 37% to 46% of unbound serum levels The in vitro octanol water partition coefficient for quinidine at physiologic pH was greater than 100 indicating that unbound quinidine should readily traverse the blood brain barrier Thus passage of quinidine into CSF appears not to be governed by passive diffusion alone Quinidine may participate in an active transport system such as that which removes certain other basic substances from CSF

We are grateful for the assistance of Ann Werner Kate Franke Lawrence J Moschitto and Dr Dean S MacLaughlin Dr MacLaughlin is supported by Grant GM 23430 to the Boston Collaborative Drug Surveillance Program Drs Reynold Spector William Oldendorf and Stanley Rapoport provided valuable critical comments

REFERENCES

1 Bleifeld, W Side effects of antiarrhythmic drugs, Naunyn Schmiedebergs Arch Pharmakol. 269 282 1971
2 Abrams, J Quinidine toxicity a review Rocky Mt Med J 70 31 May 1973
3 Greenblatt D J Antiarrhythmic agents in Drug

in a chronic alcoholic patient coincidental with a serum aprindine level of 3 μg/ml In another study, those patients developing psychosis while on aprindine had previous histories of mental illness or hypoxic brain damage[3] Other authors feel that the neurologic side effects of aprindine generally did not occur at serum levels less than 1 μg/ml without fine tremor and dizziness occurring prior to intention tremor ataxia and the other CNS manifestations[5] Here, patients reporting hallucinations had serum levels of 1 6 to 3 6 μg/ml

Our patient had no psychiatric history and on previous hospitalization both in the CCU and on the floors had never exhibited any signs of depression or bizarre behavior The sudden onset of psychosis concurrent with aprindine administration and its subsequent complete resolution after discontinuing the drug is strong evidence of drug induced psychosis The serum level of 1 05 μg/ml is only borderline therapeutic and does not approach the levels previously reported in patients with psychosis while on aprindine In addition she did not exhibit any other CNS side *effects associated with aprindine toxicity* We conclude that psychosis may appear as an isolated side effect of aprindine administration at relatively low serum levels The drug s efficacy in suppressing ventricular arrhythmias, especially in patients with the mitral valve prolapse syndrome, is reinforced It remains however an agent with significant side effects that restricts its use to patients in whom other anti arrhythmic therapy has been unsuccessful

Summary

A young woman with mitral valve prolapse and ventricular tachycardia refractory to numerous antiarrhythmics received a trial of aprindine During the course of treatment she developed a severe psychotic reaction that resolved after the drug was stopped Her psychosis was unassociated with the other dose related neurological side effects of aprindine and occurred at borderline therapeutic levels of the drug

We wish to thank Dr Thomas Rommer for referring this patient to us for the therapeutic trial

REFERENCES

1 Hagemeijer F Janse C and Hugenholtz P G Efficacite antiarythmique de l aprindine a la phase aigue de l infarctus du myocarde Acta Cardiologica (Suppl XVIII) 409 1974
2 Hagemeijer F Absorption half life and toxicity of oral aprindine in patients with acute myocardial infarction Europ J Clin Pharmacol 9 21 1975
3 Palma Gamiz U L Boedo C Lopez Pujol F S and De Uria J S Etude clinique d un nouvel anti arythmique aprindine Acta Cardiologique (*Suppl XVIII*) 361 1974
4 Breithardt G Gleichmann U Seipel L and Loogen, F Long term oral antiarrhythmic therapy with aprindine Acta Cardiologica (Suppl XVIII) 341 1974
5 Fasola A F Noble R J and Zipes D P Treatment of recurrent ventricular tachycardia and fibrillation with aprindine Am J Cardiol 39 903 1977

IMPORTANT
INFORMATION FOR AUTHORS

All manuscripts for the AMERICAN HEART JOURNAL should be sent to

Dean T Mason M D
Section of Cardiovascular Medicine
University of California
School of Medicine
Davis California 95616

Case reports

Aprindine psychosis

Glenn P Jacobs M D
Ira H Pores M D
Newark N J

Aprindine is an anti arrhythmic drug presently being used in clinical investigation for the treatment of refractory supraventricular and ventricular tachycardia The various side effects reported including agranulocytosis cholestatic hepatitis and neurological reactions such as tremor and ataxia are dose related and reversible We report here a case of acute psychosis developing at borderline low therapeutic levels of aprindine

Case report

The patient is a 29 year-old female who was in previous good health and who six months prior to thi admission developed coughing and wheezing while at work She was examined by a physician who discovered an irregular pulse and admitted her to the hospital for further ork up Initial ECG revealed frequent PVC s with coupling and the patient was admitted to the CCU for observation Evaluation by echocardiogram at that time disclosed the presence of mitral valve prolapse The electrocardiogram showed frequent I VC s and non specific ST T wave changes in Leads II III and aV with normal QT interval CBC electrolytes BUN glucose calcium magnesium cardiac enzymes arterial blood gases and ventilation-perfusion lung scan were all normal. Holter monitoring revealed frequent PVCs bigeminy trigeminy couplets and several runs of ventricular tachycardia lasting as long as 12 to 15 seconds. For control of palpitations and the arrhythmia multiple combinations of Inderal (propranolol HCl) Norpace (disopyramide) dilantin and quinidine were used. The patient was discharged on Norpace 300 mg orally every 6 hours and Inderal 100 mg orally every 6 hours.

During the ensuing 5 months she was followed as an outpatient Because of persistent ventricular tachycardia and complaints of palpitations she was readmitted to the Newark Beth Israel Medical Center for a trial of aprindine She was taking digoxin 0 25 mg daily propranolol HCl 40 mg every 6 hours and quinidine gluconate 1 tablet every 8 hours

She had not been on any other medications except for oral contraceptives which were stopped 5 months prior to admission She is the working mother of three children with no history of depression or psychosis She neither smoked nor used alcohol

Physical examination revealed a young female in no distress with an irregular pulse of 76/minute Lungs were clear Examination of the heart disclosed a non-ejection click, with a late systolic murmur on standing The remainder of the examination was unremarkable

All medication was stopped for 24 hours and the patient was placed in the CCU After baseline CBC electrolytes bilirubin SGOT SGPT alkaline phosphatate and T were obtained aprindine was started orally On day one 300 mg was given in three doses on day two 150 mg was given in two doses on day three 200 mg. was given in two doses From the fourth day she was maintained on aprindine 75 mg orally twice a day A marked therapeutic response was noted with only single PVCs on her Holter monitor tracings

On the sixth day of therapy she became extremely agitated anxious and combative She had delusions of having died in her sleep and thought she was being poisoned throu h the air conditioning At this time her physical examination was unchanged She had no tremor ataxia or nystagmus

She was seen in psychiatric consultation and was felt to be having an acute psychotic reaction possibly on a toxic basis. Her serum chemistries CBC liver and cardiac enzymes were all within normal limits An aprindine level drawn at that time was 1 05 μg/ml. (Eli Lilly Laboratories) The aprindine was withheld and over the next 3 days her mental status returned to normal

Discussion

Previous reports of hallucinations and psychosis during aprindine therapy were in patients in whom either toxic serum levels were achieved with accompanying tremor ataxia or nystagmus or in clinical situations where the etiology of the psychosis was impossible to ascertain [1] Hagemeijer and colleagues [2] in their clinical studies of aprindine in patients with acute myocardial infarctions found three patients with disorientation hallucinations and nightmares Aprindine levels were measured in two of these and were greater than 3 μg/ml Delirium tremens appeared

From the D partment of Cardi logy N wark Beth Isr el Medical Center N wa k N J

Recei ed f r publication M 8 1979
Accepted fo publication Apr 24 19 9

Reprint req ests Ira H P res M D New k Beth Isra l Medical Center 201 Lyo s A e at O borne T rr New rk, N J 0711

000?-8 03/80/090347 + 0?$00 ?0/0 © 1980 The C V Mosby Co

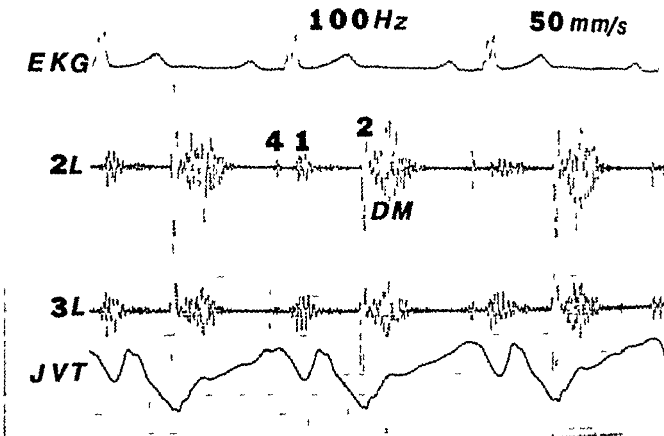


Fig 1 Phonocardiogram showing a fourth heart sound and a diastolic murmur following the pulmonic component of the second sound. JVT = jugular venous tracing

ventricle was dilated Cardiac catheterization data appear in Table I The pressure contour in the pulmonary artery was strikingly similar to that of the right ventricle consistent with severe pulmonic regurgitation Injection of contrast material in the pulmonary artery demonstrated 4 plus pulmonic regurgitation Selective injection of both the right ventricle and pulmonary artery demonstrated a 2 by 3 cm accumulation of dye in the right ventricular outflow tract which was best seen in diastole (Fig 4) The contrast material appeared to be trapped within a structure or mass A small but prominent calcification was noted adjacent to this accumulation of contrast material A tumor was judged to be present together with severe pulmonary regurgitation and surgical intervention was recommended

Significant dilatation of the pulmonary artery and right ventricular outflow tract was noted at surgery Following right ventricul ot my n tumor was found There was a small 5 mm in diam et r calcified polyp like mass on the septal side of the right ventricular outflow tract (Fig 5A) Pulmonary arteriotom r led a tricuspid pulmonic valve with the left leaflet inta t The remaining leaflets had large fenestrations occupying ximately 60% of their area (Fig 5B) The valve tissue thin and glistening The margins of the fenestrations wer h with normal endothelialization and without evidence n r previous infection Primary closure of each fen wa accomplished The postoperative course was ur All blood cultures before and at the time of surgery growth

Postoperatively the patient had a grade I/VI systo ejection murmur and a grade II/VI harsh diastolic murm along the left sternal border Neither M mode echocardiogra (Fig 2B) nor 2 D echo revealed any mass or abnorm reflectance in the right ventricular outflow tract Repe cardiac catheterization (Table I) revealed normal pulmona arterial pressure contours and 2 plus pulmonic regurgita No abnormal accumulation of contrast material occurred the right ventricular outflow tract

The patient is currently nine months postoperative an functions at full activity but continues to have physi findings of mild pulmonic regurgitation

Discussion

M mode and more recently two dimensional echocardiography have assumed paramount importance in the evaluation of intracardiac tumors The accuracy of these techniques to diagnose primary cardiac tumors as well as extra cardiac tumors is impressive Occasional reports exist in which other structures including mitral stenosis nonthrombotic masses on the mitral valve mitral valve prolapse and ventricular pacemaker wires can mimic intracardiac tumors

'Pseudo tumor' of the right ventricular outflow tract and congenital pulmonary valve regurgitation A case report*

LCDR J F Lutz MC USNR
CAPT A D Hagan MC USN
CAPT W V R Vieweg MC USN
CDR S I Thompson MC USNR
CAPT B L Aaron MC USN
San Diego Calif

In recent years M mode and two dimensional echocardiography have greatly enhanced our ability to recognize intracardiac tumors noninvasively [1-4] However the limitations as well as the usefulness of this technology warrant emphasis

Case report

This asymptomatic 26-year-old man was referred for evaluation of a heart murmur There was no history suggestive of infective endocarditis scarlet fever rheumatic fever or drug abuse Cardiac murmurs which were thought to be systolic were heard at 12 and 18 years of age

Physical examination revealed a blood pressure of 120/80/75 mm Hg The neck veins were flat at 45 degrees incline with a dominant "a" wave Carotid and peripheral pulses were full and equal and there was no evidence of cyanosis clubbing or edema The chest was clear The point of maximum impulse was in the fifth left intercostal space at the mid clavicular line The first heart sound was of normal loudness as was the second heart sound which demonstrated physiologic splitting No ejection clicks were present A fourth heart sound was best heard along the lower left sternal border There was a short high frequency mid systolic murmur and a harsh middle frequency grade III/VI diastolic murmur along the left sternal border (Fig 1) Both murmurs increased with inspiration

The chest x ray was normal The electrocardiogram demonstrated a vertical axis and was within normal limits. The M mode echocardiogram demonstrated dense echoes posterior to the pulmonic valve during diastole consistent with a right ventricular outflow tumor (Fig 2A) Other sections of the M mode echocardiogram failed to demonstrate right ventricular enlargement paradoxical septal motion or fluttering of the anterior leaflet of the tricuspid valve Wide angle two-dimensional (2 D) echocardiography (Fig 3) revealed a prominent reflectance in the right ventricular outflow tract which measured approximately 2 by 2 cm. in diameter and imaged only during diastole The motion of the structure was that of the surrounding right ventricular outflow tract The bright reflectance or "mass-like" structure was always below the pulmonary valve and demonstrated no apparent involvement of either the valve or pulmonary artery The real time 2 D echo images of the pulmonary valve were normal. In contrast to the appearance of the M mode echocardiogram the right

Table I Pre operative (column A) and postoperative (column B) cardiac catheterization findings

	A		B
	Pressure (mm Hg)	*Saturation*	*Pressure (mm Hg)*
Superior vena cava		70%	
Right atrium	a = 11	72%	a = 14
	v = 9		v = 14
	m = 9		m = 12
Right ventricle	32/11		36/12
Pulmonary artery	32/12	74%	36/16
	m = 19		m = 20
Pulmonary artery wedge	m = 10		
Left ventricle	129/13		
Aorta	129/72	96%	
	m = 96		

Hydrogen inhalation circulation time in the pulmonary artery was normal.

From the Cardiology Branch, Department of Medicine Cardiothoracic Surgery Department and the Clinical Investigation Center Naval Regional Medical Center San Diego Calif

Supported in part by the Bureau of Medicine Clinical Investigation Program

Received for publication June 4 1979

Accepted for publication Aug 16 1979

Reprint requests CAPT W V R Vieweg MC USN Head Cardiology Branch Naval Regional Medical Center San Diego Calif 92134

*The opinions or assertions expressed herein are those of the authors and are not to be construed as official or reflecting the views of the Navy Department

0002-8703/80/090349 + 06$00 60/0 © 1980 The C V Mosby Co

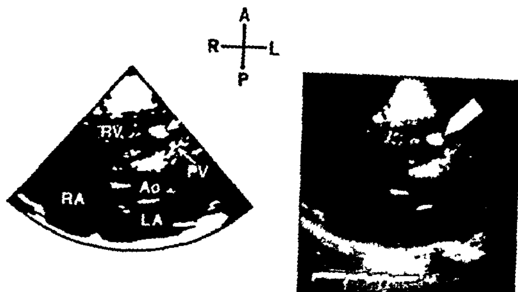


Fig 3 Two-dimensional echocardiogram of right ventricular *(RV)* outflow tract revealing dense echoes in RV outflow tract beneath the pulmonic valve *(arrow)* *RA* = right atrium *Ao* = aorta *LA* = left atrium *PV* = pulmonic valve *A* = anterior *P* = posterior *R* = right *L* = left

In retrospect the dense reflectances observed on both M mode and 2 D echo studies in the right ventricular outflow tract during diastole were generated by the 5 mm calcified polyp like mass This small lump which contained no tumor cells was thought to be consistent with a jet lesion secondary to the long standing congenital pulmonary insufficiency Because of its small size and the normal motion of the contracting right ventricle the calcium moved out of the path of the echo beam during systole

Because of beam width resolution error the mass like reflectance on M mode echo appeared to be involving or much closer to the pulmonic valve compared to what was actually found Motion and thickness of pulmonic valve leaflets were confirmed to be normal with 2 D echo and the structure in question did not involve or attach to the valve In retrospect the obvious site of calcification on fluoroscopy should have alerted the echocardiographer that the apparent mass on 2 D imaging may have been generated by the calcium

The echocardiographic interpretation error was compounded by the localized accumulation of contrast material on the angiogram in the same region of the right ventricular outflow tract This localized trapp[illegible] dye was thought to be related to [illegible] p[illegible] of mass whereas in retrospect it was [illegible] an unusual accumulation of dye amid [illegible] trabeculations of the dilated



Fig 4 Angiography of the right ventricular outflow tract seen from a lateral view demonstrating an oval accumulation of contrast material *(arrow)* beneath the pulmonary valve

outflow tract fortuitously directed by the two large fenestrations in the pulmonic leaflets There was no relationship between the small calcified lesion and the nearby accumulation of contrast material

In the absence of any other abnormality involving the pulmonic valve it is not surpris[illegible] that both M mode and 2 D echo studies revealed the valve to appear normal Echocardiography is quite insensitive to identify isolated pulmonary valve insufficiency

Isolated congenital pulmonic valvular regurgitation is a rare anomaly more frequently congen[illegible]

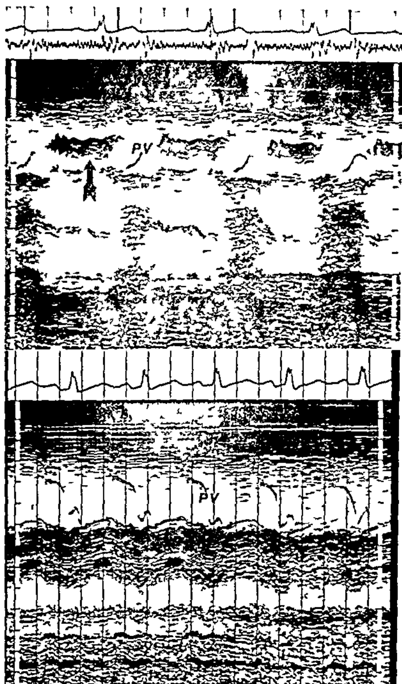


Fig 2 *A (top panel)* M mode echocardiogram of pulmonic valve showing dense echoes beneath the pulmonic valve *(PV)* during diastole *(arrow)* *B (bottom panel)* M mode echocardiogram of pulmonic valve *(PV)* postoperatively demonstrating absence of dense reflectances beneath pulmonic valve seen preoperatively The A wave amplitude is prominent

The technical problems created by side lobe artifacts of 2 D echo images and beam width resolution errors of M mode studies are well recognized It is also well known that prosthetic materials wires catheters and calcium will generate very prominent reflectances when the beam intersects them Accordingly the gain settings of the equipment must be reduced to prevent the respective structure or calcium from appearing much larger than actual size

graphic diagnosis of large left atrial tumor and extracardiac tumor compressing the left atrium Am J Cardiol 42 853 1978
7 Feigenbaum H Echocardiography 2nd ed Philadelphia 1976 Lea & Febiger Publishers
8 Chang S M mode echocardiographic techniques and pattern recognition Philadelphia 1976 Lea & Febiger Publishers
9 Kendrick M H Harrington J J Sharma R K Askenazi J and Parisi A F Ventricular pacemaker wire simulating a right atrial mass Chest 72 649 1977
10 Yoshikawa J Yoshida K Owaki T Kato H Yanagihara K Takagi Y Okumachi F and Baba K Echocardiographic features of congenital pulmonary regurgitation Jpn Heart J 19(1) 58 1978
11 Sanyal S K Hipona F A Browne M J and Talner N S Congenital insufficiency of the pulmonary valve J Pediatr 64 728 1964
12 Robbins S L Pathology Philadelphia 1967 W B Saunders Company 3rd ed
13 Ford A B Hellerstein H K Wood C and Kell B I olated congenital bicuspid pulmonary valve A Med 20 474 1956
14 Koletsky S Congenital bicuspid pulmonary v Arch Pathol 31 338 1941
15 Kissin M Pulmonary insufficiency with a supernu ary cusp in the pulmonary valve Am Heart J 12 1936
16 Pougit J M Kelly C E and Pilz C G Cong absence of the pulmonic valve Am J Cardiol 1 1967
17 Smith R D DuShane J W and Edwards J Congenital insufficiency of pulmonary valve Circul 20 554 1959
18 Ito T Engle M A and Holswade G R Cong insufficiency of pulmonary valve Pediatrics 2 1961

Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978 Therefore all manuscripts must be accompanied by the following written statement signed by one author The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C V Mosby Company in the event the work is published The undersigned author warrants that the article is original is not under consideration by another journal and has not been previously publi hed I sign for and accept responsibility for releasing this material on behalf of any and all co authors Authors will be consulted when possible regarding republication of their material



Fig 5 *A* Small calcified mass *(arrow)* found at surgery on the septal side of the right ventricular outflow tract *B* Pulmonary valve at time of surgery demonstrating large fenestrations in pulmonary valve leaflets with normal surrounding valve tissue

ital pulmonic regurgitation is associated with a ventricular septal defect with or without pulmonic stenosis[11] The large fenestrations causing pulmonic regurgitation in our case have not been reported previously Fenestrations are usually seen as oval defects 0 1 to 0 3 mm in diameter and are of no hemodynamic importance[1] Common causes of congenital pulmonic regurgitation include bicuspid valve[1] supernumerary valves[11] and agenesis of the valve[1] The findings at surgery excluded infective endocarditis as the cause of pulmonic regurgitation in our patient Isolated congenital pulmonic regurgitation of a mild degree as presently found in our patient is associated with a very favorable prognosis

Summary

The M mode and 2 D echocardiographic features of an unusual case of a pseudo tumor of the right ventricular outflow tract are reported The unique pathologic findings of the pulmonary valve with congenital fenestrations and the clinical implications of this pseudo tumor are discussed Whenever calcification is noted at fluoroscopy to exist in a region or structure being evaluated by echocardiography caution must be taken to avoid overestimating the size Indistinct dense reflectances without specific motion or appearance of a mass further helps to distinguish the reflectances from an actual structure of significance Furthermore all clinical angiographic and echocardiographic information must be interpreted together when either the angiogram or the echocardiogram is confusing and potentially misleading

REFERENCES

1 Wolfe S B Popp R L and Feigenbaum H Diagnosis of atrial tumors by ultrasound, Circulation 39 615 1969

2 Popp R L and Harrison D C Ultrasound for diagnosis of tumor Ann Intern Med 71 785 1969

3 Ports T A Schiller N B and Strunk B L Echocardiography of right ventricular tumors, Circulation 56 439 1977

4 Lappe R L, Bulkley B H and Weiss, J L Two-dimensional echocardiographic diagnosis of left atrial myxoma Chest 74 55 1978

5 Ports T A Cogon J Schiller N B and Rapaport E Echocardiography of left ventricular masses Circulation 58 528 1978

6 Yoshikawa J Sabah, I Yanagihara K, Owaki, T., Kato H, and Tanemoto K Cross-sectional echocardio-

their action as being anti infarct by an analogy with the term anti arrhythmic

Definitions Myocardial Infarction and Infarct Size

Infarct size is difficult to define because both infarct and size are not necessarily clear entities The history of the use of the term myocardial infarct has been traced by Wartman[10], it was first used in 1689 to indicate a vessel stuffed in —i e occluded Later the association of regional tissue necrosis and vascular occlusion came to be called infarction i e massive regional necrosis caused by obstructive arteriosclerosis [10] Histologically there was a coagulation necrosis But room was also left for the occurrence of noncoronary necrosis [10]

Subsequently the tight association between an occlusive lesion and regional necrosis has become controversial Thus some evidence shows that (1) histologic features of coagulation necrosis can occur without associated acute occlusion especially but not exclusively in smaller infarcts or subendocardial lesions[11 12] and that (2) in addition to coagulation necrosis other types of necrosis can be recognized in particular contraction band formation or myocytolysis [13] which occurs around the border of human infarcts[1] and may be due to catecholamine induced hypercontraction of the cell [14] Other authors hold that the causative thrombus can regularly be found if searched for with sufficient care and vigor [15 17] Thus the relation between the thrombus and the histological lesion is by no means settled [18] One recent authoritative view is that the thrombus although found in just over half (60%) of the patients dying with acute transmural infarction is usually *absent in patients dying soon after the onset of* symptoms [19] Thus (1) myocardial infarction need not necessarily be associated with a vascular occlusion lesion nor need the histological damage be limited to the classical coagulation necrosis and (2) the term infarct therefore touches on certain very controversial vascular and histologic definitions

Nor is the use of the term infarct size any less free from problems of definition In the strict sense the volume of infarcted tissue should be expressed as a percentage of the total but experimental studies have generally used indirect indices such as the number of sites with electrocardiographic evidence of ischemia (ST elevation) or the degree of enzyme (creatine kinase) depletion, and only seldom has true pathological size been quantified Pathological quantification is made more difficult by the heterogeneity of the lesion with an admixture of living and dead cells [10] Quantification is more easy using the degree of myocardial depletion of creatine kinase which has however, been linked only to the severity of coagulation necrosis [1] while the relation if any, to myocytolysis (hypercontracted dead cells) remains to be determined It should also be noted that the size of the infarct assessed 24 hours post ligation is not necessarily the same as that of the eventual scar (scar size) Finally even if there were well defined pathologically uniform lesions infarct size could never be directly measured in patients except in those who died

However a number of indirect indices of infarct size have been proposed for use in patients The evaluation of *ST changes* from multiple leads as a blanket [0] or a computerized combined signal only indicates trends in the development of ischemia not infarct size [3] and is open to a *multitude of theoretical objections* [2] as well as not correlating with infarct size measured by enzyme release [3] The critical importance of distinction between an effect on ischemia and on infarct size is shown by the experience with mannitol which reduced ischemia and even features of histological necrosis after 40 minutes occlusion of the coronary artery but which had no effect when given during prolonged coronary occlusion [4]

Evaluation of *precordial Q waves* has been proposed by Hillis and associates [5] and by Selwyn and Shillingford [6 6] In patients past the acute stage of myocardial infarction the number of abnormal Q waves on a 35 lead precordial blanket could accurately predict the extent of left ventricular dysfunction as shown by cardiac catheterization and angiography [7] Askanazi and colleagues found that the extent of early ST elevation can predict the severity of subsequent Q wave formation as judged by the extent of R wave loss Their studies were carried out with conventional ECG leads and appear to hold promise for a simple method of assessing the effects of anti infarct agents which should decrease the eventual rate of Q formation for a given degree of early ST elevation

The rate of release of the enzyme creatine

Review

Myocardial infarct size Part I Basic considerations

Lionel H Opie M D
Cape Town South Africa

The concept of infarct size has been introduced into general medical management by the studies of Braunwald Maroko and their associates Reduction of infarct size and protection of the ischemic myocardium have become household terms in the vocabulary of most practicing cardiologists in the United States[3] The concept of modification of infarct size rests in part on three important observations showing that the full development of the infarct process may be measured in hours and days rather than in minutes and seconds First full development of the complete pathological process in animals may require several days Secondly experimentally produced coronary artery thrombi grow for at least 72 hours[5] Thirdly clinical observations show that reinfarction (or extension) of infarction occurs in many patients frequently after their discharge from an intensive care unit A further complication is expansion of the infarct which occurs chiefly in large transmural and not in small subendocardial infarcts in keeping with the importance of limitation of infarct size

Although the clinical syndrome of acute myocardial infarction will be the prime object of this review it must be stressed that a *pathological* diagnosis of infarction can only be made in the presence of necrosis whereas a *clinical* diagnosis can frequently be made in the early hours when the actual necrotic process is still developing Thus a more appropriate initial clinical diagnosis would be developing or impending myocardial infarction[9] This review first considers the possible initial events in developing myocardial infarction and then the factors promoting the progression from ischemia to infarction Thereafter the effects of therapeutic agents are considered

One hypothesis is that during the process of development of infarction there is an imbalance between the myocardial oxygen supply and demand Factors increasing the oxygen demand are held to worsen the ultimate infarct size Conversely factors improving the oxygen are held to improve the ultimate infarct size But confusion arises from the delicate balance between salutary and harmful effects of the specific interventions Thus for example reduction of the oxygen demand of the heart by reduction of the afterload also reduces the coronary perfusion pressure and the latter effect may reduce the collateral blood supply to the infarcting myocardium At the same time the vast number of agents available to reduce infarct size has become bewildering to the average cardiologist and the principles of choice obscure

It could legitimately be argued that infarct size reduction in patients has no place in our present state of knowledge until the results of randomized double blind studies with long term follow up become available However considerable endeavor has been put into animal experiments to show that infarct size reduction is possible and there has been much thought and discussion about methods of indirectly assessing ischemic injury and infarct size in man The topic dominates many discussions at cardiological meetings Therefore it seems appropriate to review present knowledge of the principles involved and the chief agents being evaluated in patients Because the specific aim of those agents is the capacity of limit infarct size it seems appropriate to designate

From the MRC Ischa m Hea t Disease Rese rch Unit D partm nt of Medicine Groote Schuur Hospital nd Uni ersity of Cape Town Cape Town South Afri

Recei ed for publicati n Dec 29 19 8

Reprint requests D Lionel H Op Dept of Medicin Medical School, Observ tory 7925 Cape S uth Afric

0002-8703/80/090355 + 18$01 80 0 © 1980 The C V Mosby Co

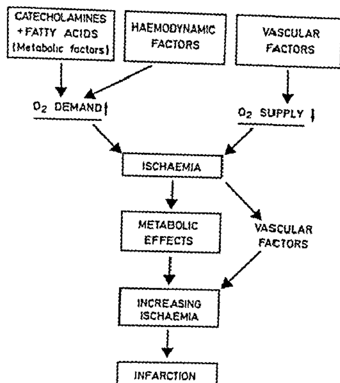


Fig 1 Ischemia can be caused by (1) a reduced oxygen supply resulting from vascular factors (see *Fig 2*) or (2) by an increased oxygen demand resulting from hemodynamic (see *Fig 3*) or metabolic factors (see *Fig 4*) Ischemia once produced can in turn produce metabolic changes that increase ischemic damage and eventually cause infarction (see *Fig 5*) Proton production may have a special role in increasing the ischemic damage (see *Fig 6*)

ischemia and those factors causing the transition from ischemia to infarction and to consider whether those processes are amenable to therapeutic intervention

Initial events in acute myocardial infarction

Animal models of myocardial infarction have generally used either (1) acute occlusion by ligature of otherwise healthy coronary arteries frequently in open chested anesthetized dogs or (2) massive injections of catecholamines The former procedure produces transmural myocardial infarction and the latter procedure produces subendocardial necrosis Even when more sophisticated techniques such as the electrical production of arterial thrombi [illegible] occlusion by a screw clamp impactor [illegible] balloon or embolization by glass balls [illegible] there are still many critical differences [illegible] the situation in patients with acute myocardial infarction

The ideal model [illegible] be a subhuman primate with spontaneously [illegible] severe coronary atherosclerosis superimposed thereon would [illegible] the primary event known to occur in man [illegible] that primary event still remains unknown [illegible] those many patients with heart attacks who [illegible] within the first hours and die an arrhythmic death[38,39] the initial event in such deaths does not appear to be an occlusive thrombus[40] except when there is bradyasystolic cardiac arrest[41] [illegible] role for evanescent thrombi or platelet aggregations[42] cannot be excluded If coronary arterial spasm should play a major or even a contributory role in heart attacks[4] then the production of [illegible] suitable animal model becomes even more complex

Nevertheless there is widespread recognition that very early lesions both in animals and [illegible] man have a variable and possibly predominant element of reversibility (ischemia) whereas the eventual lesion is irreversible (infarction) It is therefore appropriate to concentrate firstly on the factors that might produce ischemia and then on those factors underlying the transition from ischemia to infarction

Ischemia can be caused by impaired delivery of oxygen by poor blood supply as a result of *vascular factors* (Fig 1) Alternatively the oxygen demand can be enhanced by *hemodynamic* or *metabolic factors* and ischemia could result especially in the presence of some degree of reduced coronary flow Metabolic factors may also act in other ways such as promotion of membrane damage Ischemia once produced can in turn provoke metabolic and vascular changes which aggravate the ischemia and ultimately produce infarction (Fig 1) The production of ischemia by vascular hemodynamic and metabolic factors will now be considered

1 Role of vascular factors (Fig 2) Traditionally arterial obstruction has been the event initiating ischemia of sufficient severity to lead ultimately to acute myocardial infarction and mechanical block has been regarded as the most important cause of vascular obstruction [2] In addition to thrombosis arterial obstruction may be caused by embolism formation of platelet aggregates and by plaque rupture or by formation of a thrombus on a preexisting plaque[4] But the causative role of such factors especially of the thrombus is controversial Coronary vasospasm is coming to the fore not only as a cause of angina at rest but of infarction Little is known about the mechanism of arterial spasm[43] That coronary

kinase (= CK = creatine phosphokinase = CPK) has been studied extensively by Sobel's group.[29] *The theory is that the accumulation of CK in the blood derives from the infarct*, provided that no intramuscular injection has been given, in which case the cardiospecific isoenzyme MB CK should be used. In practice numerous problems arise including the high rate of enzyme destruction within the infarct zone and the difficulty of assessing the influence of factors altering the rate of removal of CK from the circulation.[1] Nevertheless infarct estimation by the CK method is a clinically useful procedure.[31] Furthermore, by making certain assumptions, the expected infarct size for any given patient can be determined from the initial CK values before the infarction and can be compared with the actual infarct size after interventions.[3] Although the latter procedure is perhaps most open to theoretical objections, nevertheless it has been used to show the beneficial effect of afterload reduction[1] and the harmful effects of digitalis given to patients without severe heart failure.[33] A practical problem with this technique is the requirement for frequent blood sampling over a prolonged period.

Radionuclide techniques are particularly popular at the moment. For example, myocardial scintigraphy with 99m technetium glucoheptonate correlates well with infarct weight in dog infarcts.[34] In patients who died with large myocardial infarction and who had been studied by 201 thallium during the acute phase, there was good correlation between scintigraphic and postmortem estimation of infarct size. But even by using a very sophisticated technique ([1]C palmitate of half life 20 minutes giving a "cold" infarct scan and quantified by positron emission transaxial tomography[1]), the results are not at present accurate enough for assessing the effects of therapy.

Thus infarct size cannot be directly measured but can only be indirectly assessed by trends in the electrocardiogram, by the patterns of enzyme release, and possibly by radionuclide techniques. Therefore, "infarct size" is not only a somewhat debatable term but is difficult to measure. The term has, however, firmly introduced itself into modern cardiological practice.

Hereafter the term "infarct size" as applied to patients will be taken to refer to such indices of infarct size rather than to accurately measured infarct size.

Differentiation between ischemia and infarction

In the original and classic paper by Maroko, Braunwald, and co-workers, the extent and severity of *epicardial ST segment elevation* 15 minutes after coronary artery ligation in the dog could be used as a predictor of the severity of myocardial cellular damage 24 hours later, as assessed either by histologic damage or by the extent of depletion of the enzyme creatine kinase (= creatine phosphokinase). It was reasoned that any increase in the degree of enzyme loss and histologic damage must indicate that the ultimate infarct was bigger and thus infarct size had increased, although the latter was never quantified in a precise pathologic sense. The Braunwald group thereafter meticulously measured both ST elevation and enzyme depletion before concluding that a variety of agents altered infarct size. Other investigators using the same model sometimes measured the ST elevation at 15 minutes and omitted the enzyme and histologic data. In patients it was a small step towards equating effects on precordial ST elevation with effects on infarct size. Although there is a relation between early ST elevation and later QRS changes, it must be understood that ST elevation is an index of acute ischemic injury provided that other causes are excluded, whereas it is the loss of R wave and formation of the Q wave that more closely corresponds to coagulation necrosis, i.e., infarction. The *difference between ischemia and infarction* is that the former is a reversible decrease in blood flow severe enough to have metabolic consequences such as depletion of ATP and anaerobic metabolism[1]—the latter is the irreversible development of tissue necrosis.

Logically, *efforts to limit infarct size in patients* would therefore be aimed at (1) countering the initial event causing ischemia and (2) countering those events causing the progression from ischemia to infarction while (3) in no way impeding the process of wound healing and scar formation. Furthermore, the effects of any such therapeutic procedure should be capable of assessment by a clinically feasible method of measuring infarct size. But infarct size cannot be assessed with complete confidence nor has its reduction yet been shown to be beneficial to the patient. Assuming that evidence will be forthcoming on the effect of limitation of infarct size in patients, it becomes logical to examine the production of

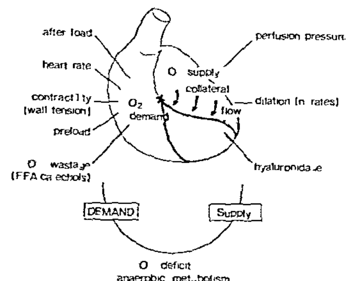


Fig 3 *Hemodynamic factors of importance in the genesis of ischemia. In regional ischemia (infarcting myocardium) there is a balance between the oxygen demand and the oxygen supply The oxygen demand exceeds the oxygen supply and there is an energy deficit. The oxygen demand depends largely on the contractility of the heart, the heart rate and the afterload but metabolic factors may play an important role "Oxygen wastage" refers to those metabolic processes which impair the conversion of oxygen taken up to ATP available for contractile purposes. The oxygen supply depends largely on the collateral flow which in turn depends on the difference between the coronary perfusion pressure and the intramyocardial pressure, and the degree of coronary vasodilation (which may be possible by increased use of nitrate) It is also possible that hyaluronidase increases the permeation of nutrients brought to the infarcting tissue by the collateral flow (Reproduced by permission of Postgraduate Medical Journal.)*

restoration of normal blood flow to the ischemic zone whether surgically or by reversal of experimental occlusion would inevitably bring about an improvement Indeed that assumption underlines the recommendation of a recent panel that acute coronary occlusion should be treated aggressively by coronary bypass as soon as possible and within [illegible] hours of the event [illegible] However reperfusion after 40 minutes of experimental coronary ligation greatly accelerates ischemic damage[54] and in [illegible] promotes calcium uptake[5] with harmful [illegible] mitochondria[55] After 90 minutes of severe [illegible] ischemia this capacity for calcium up[illegible]ochondria is lost presumably because [illegible] of mitochondria damage[56] and it [illegible] presumably be safer to reperfuse However [illegible] situation in patients with infarction with [illegible] degrees of coronary occlusion variable collateral circulation and possibly the further complication of arterial spasm cannot readily be assessed The occurrence of contraction band necrosis following coronary artery bypass graft surgery may reflect re[illegible] damage It would seem prudent to bear in mind that reperfusion may be harmful especially in the early phases of ischemic damage while late reperfusion may not be successful

Once ischemia has developed a further series of events (summarized in Figs 2 and 4) can be provoked to produce increasing ischemia [illegible] ultimate infarction

2 Role of hemodynamic factors (Fig 3) The hemodynamic factors controlling the oxygen uptake of the heart are well established[illegible] include the afterload (approximately represented by the arterial systolic pressure) the heart rate and the contractility of the heart The preload plays a lesser role because volume work is not so energy requiring as pressure work[5] However an increased preload could further dilate a fail[illegible] myocardium thereby increasing the wall tension and hence the oxygen demand It is proposed that these factors could (1) produce ischemia in the presence of a compromised blood supply and (2) promote the transition from ischemia to infarction and increase infarct size[illegible]

That such hemodynamic factors can influence the myocardial oxygen uptake is firmly established That they could influence the progression from ischemia to infarction depends on the hypothesis that there is a *balance between the oxygen supply and demand* of the ischemic zone (Fi[illegible]) which can be tipped in either direction with consequent sparing or increased injury to the critically jeopardized or vulnerable cell[illegible] their ultimate survival or necrosis This point of view calls for (1) the existence of a zone of intermediate blood supply (2) a collateral blood supply to the severely ischemic tissue and (3) the persistence of some contractile activity in ischemic tissue The existence of tissue with these intermediate properties has been held to constitute a *border zone* Moving inward from the visible edge of the cyanotic area produced by coronary artery ligation severe and progressive derangements of metabolism flow and electrocardiographic changes have been found [illegible] (see also reference of Hearse and colleagues) The [illegible] ischemic tissue and the border zone in the [illegible] also retain some contractile properties [illegible] In the

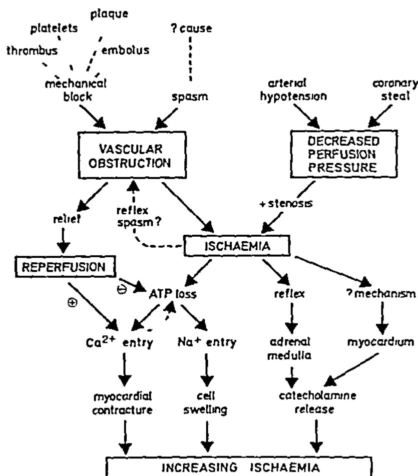


Fig 2 The classical cause of ischemia is vascular obstruction caused by a mechanical block, the latter in turn generally resulting from a thrombus. However coronary artery spa m may also play a role Either by lysis of the thrombus or by relief of spasm reperfusion may take place with decreased loss of ATP (impro ed oxygenation) but increased entry of calcium which can aggravate ATP loss Ca entry is held to be causative in the development of ischemic contracture which increases ischemia Ischemia can also provoke cell swelling and/or catecholamine release which also increase the severity of ischemia A decreased coronary perfusion pressure especially in the presence of coronary artery stenosis may be another theoretical cause of ischemia.

occlusion could cause reflex vasospasm through an adrenergic mechanism was suggested by Grayson and colleagues although their method of measuring coronary flow has now been superseded

Experimentally the degree of *collateral circulation* influences the extent and severity of the infarction process in the presence of a well developed collateral circulation coronary occlusion may have no effects Much attention has been paid to the possibility that part of the beneficial effect of nitrates in decreasing the severity of ischemia could be by augmentation of collateral flow in animals with either acute coronary occlusion or chronic coronary narrowing [50] In patients collaterals would be required to deliver the therapeutic agent to the ischemic zone which could explain why Gold and associates [1] found a beneficial effect of propranolol especially in those patients with angiographically demonstrable collateral vessels Theoretically the presence of collaterals should limit the severity of infarction in man although Baroldi and Scomazzoni[55] have argued to the contrary on the basis of postmortem dissection and case anal of the coronary circulation in mate However they did not quant t size

It might be supposed tha sion

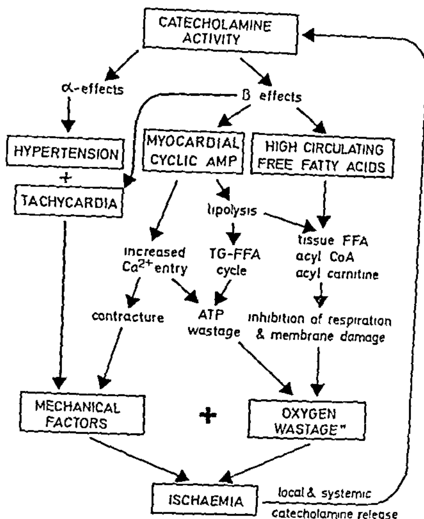


Fig 4 Catecholamines can increase ischemic injury by (1) mechanical factors such as hypertension (chiefly an α-effect) and/or tachycardia (chiefly a β-effect) (2) promotion of ischemic contracture with decreased blood flow as a result of increased calcium entry and (3) metabolic effects The latter include the effects of increased circulating free fatty acids and increased cardiac lipolysis which may cause (1) metabolically futile cycles such as the postulated triglyceride free fatty acid (see Opie) and (2) accumulation of tissue lipid metabolites These lipid changes lead to oxygen wastage (Section 2 of this report) through mechanisms not yet well defined Once ischemia is established generalized or localized release of catecholamines can lead to further catecholamine activity and a metabolic vicious circle TG = triglyceride FFA = free fatty acid Acyl CoA = long-chain acyl CoA eg palmityl CoA

intracellular passage of a macromolecule horse radish *peroxidase* An effect on cell permeability may explain why low doses of noradrenaline could induce enzyme release from the isolated heart even in the absence of major loss of high energy phosphate compounds although it remains true that high doses of catecholamines cause substantial depletion of energy as first pointed out by Fleckenstein

The effect of catecholamines on *lipolysis* warrants further consideration The myocardial oxygen consumption in a catecholamine stimulated heart can be reduced by about 30% by an antilipolytic agent When the metabolic "oxygen wastage" caused by noradrenaline is inhibited by an antilipolytic agent then ST segments over the ischemic myocardium fall rather than rise Furthermore when an inotropic stimulus equivalent to that of isoprenaline is applied to the ischemic heart by glucagon or by calcium then there is less epicardial ST segment elevation Dopamine is also a fatty acid mobilizing agent

chemic zone flow must be reduced to zero efore oxidative metabolism ceases[61] hence the emonstration of at least some collateral flow in nimal models[61 65-67] and in some patients with cute myocardial infarction[51] supports the oxy en balance theory The existence of a clearly efined border zone albeit narrow implies that herapeutic salvage of that zone could decrease he ultimate infarct size by between 35% and 65% hese are rough calculations but give an idea of nagnitude[61]

However the *oxygen imbalance hypothesis an be criticized* Chance s group [?] has argued hat the gradients for oxygen are very steep and hat mitochondria respond to oxygen in an all r none fashion thus the oxygen border zone is xtremely narrow Furthermore 24 hours after oronary ligation the border as defined by mea urements of tissue creatine kinase is narrow and consists of a mixture of normal and abnormal cells Such arguments can be countered Thus even the Chance model allows for the existence of an intermediate cell [64] and the absence of a border zone at 24 hours does not exclude one at 25 minutes Nevertheless it must be noted that the border zone concept has been challenged

A major criticism of the oxygen supply versus demand theory is that in very few studies if any have both the oxygen uptake and the infarct size been measured under the influence of a thera peutic agent And even if the over all myocardial oxygen uptake were known that does not neces sarily reflect changes in a similar direction in the critical oxygen uptake of the border zone However on the whole agents which *theoretically* change the myocardial oxygen uptake have sub sequently been shown to change the infarct size in a similar direction[1]

3 Role of catecholamines (Fig 4) Raab and associates[71] made the basic observation that the infusion of catecholamines could precipitate fea tures of regional ischemia in an experimental preparation with compromised coronary circula tion Since then much evidence has supported the concept that catecholamines can exaggerate the degree of myocardial ischemia although dose effects and the relative balance between α and β effects cause complex results [?] Thus pure β stimulation by isoprenaline increases ischemic injury[6] and infarct size in dogs whereas com bined α and β stimulation by noradrenaline decreased the extent of ischemic injury presum ably because the beneficial effects of an increased coronary perfusion pressure outweighed the harmful effect of an increased afterload[?] or because other unspecified beneficial effects could be achieved by low doses of noradrenaline in the absence of systemic hypertension[?] and despite elevation of circulating free fatty acids [?] But it must not be assumed that α-effects are necessari ly beneficial Methoxamine given in similar doses decreased infarct size in one series[1] and exagger ated ischemic injury in another[6] These effects of dosage and of comparative stimulation of α and β receptors are not yet well understood

β-effects of catecholamines appear to be harm ful to the ischemic myocardium and the mecha nisms involved may include (1) an increased heart rate[? ?] (2) increased circulating free fatty acids [?] and (3) the effects of an increased intracellular cyclic AMP level Cyclic AMP is fundamentally involved with the *entry of calcium ions into myocardial cells*[77] *Increased entry of* calcium ions could in part explain the phenome non of oxygen wastage found in a classical study by Lovatt Evans[73] Uptake of calcium by mitochondria is energy requiring and occurs as an alternative to oxidative phosphorylation[79] In creased calcium entry may also be harmful by provoking myocardial contracture with compres sion of the blood supply Another postulated mechanism whereby cyclic AMP in excess could harm the heart is by *stimulation of lipolysis* in the heart the resultant liberation of long chain free fatty acid could in the presence of α glycerophos phate derived from glycolysis [?] promote re-esterif ication of fatty acid to triglyceride with the operation of a triglyceride-fatty acid cycle[77] which is energy wasting

Yet another mechanism to produce oxygen wastage could be by *accumulation of products of fatty acid metabolism* in the tissue (tissue free fatty acid acyl CoA and acyl carnitine) these compounds can inhibit respiration[83] and cause membrane damage Even if oxygen does reach the ischemic mitochondria it need not be efficiently used Thus there are problems not only with the oxygen supply but also with the conversion of the available oxygen to energy

Besides mechanical factors and oxygen wast age catecholamines may also act by *increasing cell permeability* which occurs within 10 minutes of the exposure of the healthy animal heart to high doses of catecholamines as evidenced by the

cholamines on the infarction process Isoproterenol (0.25 to 0 50 µg/kg /minute) increases depletion of myocardial creatine kinase an indirect marker of the extent of necrosis[3] there is enzyme depletion in those sites which are not involved by coronary occlusion alone—i e the infarct has extended The dose of isoproterenol is similar to the estimated rate of secretion of catecholamines in patients with acute myocardial infarction[84] Even spontaneous rates of secretion of adrenaline *after coronary ligation in dogs are able to promote* damage away from the ischemic zone as shown by histochemical changes[93] In the isolated rat heart noradrenaline 10 M or higher is able to induce ultrastructural changes including hypercontracted cells[11] a type of lesion found especially around the edge of the human infarcts[1] and presumably also the result of catecholamine secretion

In high doses catecholamines can produce large scale infarct like necrosis even in the total *absence of coronary arterial narrowing*[94] Whether such massive doses of catecholamines could ever be secreted in response to extreme stress or other factors and hence account for some cases of infarction occurring without coronary artery disease is a matter of speculation

If however catecholamines can initiate or extend ischemic injury and ischemic injury can provoke release of catecholamines then a harmful vicious circle would be set up (Fig 4)

Progression from ischemia to infarction (Fig 5)

At a cellular level the harmful effects of ischemia are a combination of (1) poor oxygen delivery leading to depressed mitochondrial production of ATP and an accumulation of fatty acid metabolites and (2) poor washout of lactate protons and carbon dioxide which can all contribute to the severity of ischemic damage

1 Effects of poor oxygen delivery From the clinical point of view large scale enzyme release from the heart is virtually synonymous with cell necrosis—i.e myocardial infarction as opposed to other chest pain syndromes hence it would be useful to establish which metabolic events underly the liberation of enzymes from the heart In a number of simpler model *ATP depletion* can be related to the extent of enzyme release Thus the extent of fall of tissue ATP in the perfused anoxic dog heart correlates very well with the amount of enzyme released However in regional ischem (developing experimental myocardial infarct substantial tissue depletion of ATP can occu. 1 minutes after ligation before the tissue conte creatine kinase had decreased[96] More probab may be a subcompartment of ATP more re accessible to the cell membrane which h special role in the maintenance of cell membra integrity as argued by Bricknell and Opie[97] ATP is produced by glycolysis and the e is go *electrophysiological evidence for the role of* ATP in another membrane associated eve namely the production of the normal act potential Thus increased provision of glycol ATP may be one way whereby glucose is a n favorable fuel for the infarcting myocard. than is fatty acid

The observation that glucose decreased a free fatty acid increased enzyme release from t coronary ligated rat heart[99] is consonant with t above hypothesis but by no means provides di evidence In fact the beneficial effects of glucos and the harmful effects of fatty acids extremely complex In severely ischemic ti the rate of glucose uptake and glycolysis inhibited by the severity of the ischemia hence the above relationship probably hold o for mildly or moderately *ischemic tissue* and for severely ischemic tissue

The mechanism of *fatty acid toxicity* incl the intracellular accumulation of free fa acid[10] acyl CoA[3] acyl carnitine[1] and ly phospholipid Early work stressed the pos ity that accumulation of free fatty acid in tissue (secondary to impaired oxidation) co cause uncoupling and thereby "oxygen wa age more recently accumulation of the ac vated fatty acid metabolite long-chain acyl Co *has been found* and emphasized as a cause impaired utilization of oxygen so that tran ADP into the mitochondria is blocked as transfer of ATP outwards However acyl Co accumulation should depress mitochondrial o gen uptake whereas it is usually "oxygen wa tage which is *held to be* an effect of exc provision of fatty acids during ischemia (Opie)

Of the other effects of fatty acid metabol those on the membrane are a rather nonspec but nevertheless important effect which co contribute to lysosomal *activation* (see lite Inhibition of the membrane ATPase (Na /K

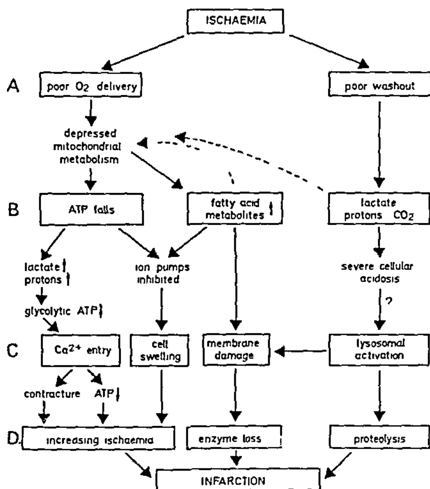


Fig 5 Proposed metabolic mechanisms whereby ischemia can produce infarction *Panel A* shows the two major effects of ischemia namely poor O delivery and poor washout of metabolites *Panel B* proposes that depressed mitochondrial metabolism results in decreased production of ATP and accumulation of fatty acid metabolites (see *Fig 4*) which are normally metabolized in the mitochondria Anaerobic metabolism causes accumulation of lactate and protons (the latter from breakdown of ATP) and continued residual respiration causes accumulation of CO *Panel C* proposes that decreased production of glycolytic ATP (a result of accumulation of lactate and/or protons) results in increased calcium entry Inhibition of ion pumps by lack of ATP and by inhibition of fatty acid metabolites results in sodium and water retention and cell swelling Fatty acid metabolites also probably cause membrane damage which may also result from lysosomal activation as a result of a severe cellular acido is or possibly as result of other mechanisms such as ATP depletion [20] *Panel D* proposes that the final events leading up to infarction may be increasing ischemia caused by ischemic contracture and cell swelling enzyme loss from membrane damage and proteolysis from lysosomal activation [29]

and increases ischemic injury more than an equivalent inotropic response obtained by calcium That oxygen wastage may exaggerate the effects of ischemia in man is suggested by the finding that in patients with coronary artery disease increased fatty acid uptake accounts for half of the increase of myocardial oxygen uptake which results from catecholamine stimulation the other half being due to tachycardia

In patients with acute myocardial infarction plasma catecholamine values are about 1 to 5 µg/L plasma (see Vetter and colleagues[90]) Such concentrations greatly increase ischemic damage in isolated rat hearts The cause of the increased catecholamine concentrations is not clear but may include psychological stress (see Opie[7]) and reflexes originating in the border zone of the infarcting tissue[8]

The data reviewed thusfar indicate complex effects of catecholamine stimulation on *ischemic* injury with the majority of effects being harmful Less work has been done on the *effects of cate*

before there is total depletion of energy Once taken up calcium can accumulate in the mitochondria and can contribute to the development of ischemic contracture usually an irreversible event[56] *More direct evidence for the postulated* role of calcium in irreversibility has been obtained with a lanthanum probe lanthanum is a trivalent ion with properties resembling those of calcium but not normally found within the cell With progressive hypoxia of the cat papillary muscle, lanthanum can be found at intracellular sites of high calcium affinity as ultrastructural changes develop after 2 to 3 hours of hypoxia[106]

However in experimental infarcts in dogs it is doubtful that massive calcium uptake is the critical event accompanying or causing irreversibility, because (1) scans for ^{99}m technetium stannous pyrophosphate are negative 7 hours after occlusion but strongly positive after transient occlusion[107] (2) uptake when found is especially localized to the border rather than to the central zone of the infarct[08] and (3) the uptake of the label does not appear to be directly related to the severity of necrosis[1] The effectiveness of calcium antagonist drugs in reducing the size of experimental infarcts[110] also does not prove the role of calcium in the pathogenesis of infarction because such drugs have multiple effects including for example relaxation of the coronary arteries

In patients increased calcium uptake does not *appear to occur very soon after the induction of ischemia by coronary vasospasm as shown by the* fall rather than the rise of dp/dt max in patients during an episode of ST elevation Nevertheless increased calcium entry may be an important initial event in the pathogenesis of other types of myocardial ischemia as suggested by Harris[8]

Thus although increased uptake of calcium into the heart cell is generally held to be an *adverse effect of ischemia and could help to* promote or cause permanent damage especially after reperfusion yet the evidence incriminating calcium is not yet firm and the use of calcium antagonist drugs is still in the early stages of investigation

2 Effect of poor washout There are major metabolic differences between hypoxia with maintained cell perfusion (eg depriving a perfused heart of its oxygen supply) and ischemia (with poor washout plus metabolite accumulation) The classic effect of poor washout is the accumulation of *protons* (Fig 6) for example from anaerobic glycolysis with ATP breakdown or from a variety of metabolic cycles which can also produce protons[8] Although severe acidosis *must be harmful to the cell* some evidence[11] [11] suggests that milder acidosis can protect the hypoxic cell by keeping out calcium (protons and calcium ions can compete for superficial binding sites)

Less well publicized are the effects of accumulation of other metabolites Thus retention of *carbon dioxide* partially as the result of continued residual respiration[64] may contribute to *impaired contractile activity soon after coronary* artery ligation[112] *Lactate* accumulation may help inhibit glycolytic flux[114] and thereby minimize the beneficial effect of provision of glucose in zones of severe ischemia Lactate may also contribute to mitochondrial damage and may shorten the action potential duration[11] [115] Finally accumulation of *NADH* in the mitochondria and cytoplasm as an effect of impaired oxidative metabolism will *depress citrate cycle activity*[8] and impair the capacity to use such oxygen as is available This mechanism together with mitochondrial depression induced by acyl CoA could explain why the cell can undergo metabolic deterioration even though oxygen may still be reaching the infarcting tissue by collaterals[8]

A cogent hypothesis linking accumulation of metabolites with cell death is the *lysosomal hypothesis* according to which ischemia causes *accumulation of protons* and of membrane active fatty acids which in turn reduces membrane integrity including that of the lysosomes Thereafter lysosomal enzymes leak out[117] cellular constituents including critical components of the cell membranes are attacked by these lysosomal enzymes and cell necrosis is initiated or accelerated[11] Although it cannot be stated with certainty that lysosomal changes are the cause and not the result of a critical stage in myocardial cellular damage yet there is a coincidence in time between lysosomal activation and the appearance of ultrastructural changes of irreversibility[1] Further weight *is given to the* lysosomal hypothesis by the effects of methylprednisolone and glucose in stabilizing lysosomes and in reducing ischemic or hypoxic damage in a variety of models[11] [21] At present the side effects of these agents in impairing wound healing *limit* their testing in man but the possibility of new analogs without

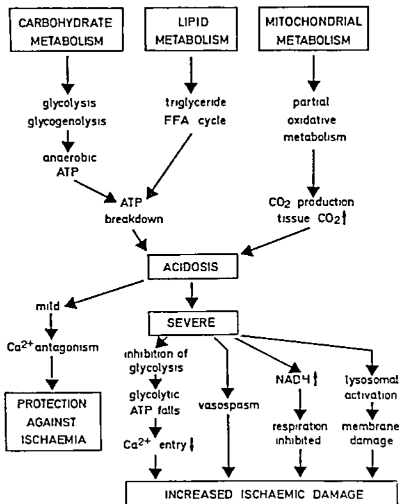


Fig 6 During ischemia protons can be produced as result of carbohydrate or lipid metabolism or mitochondrial respiration The mechanisms involved are (1) activation of glycolysis with production of anaerobic ATP and (2) activation of triglyceride breakdown with simultaneously an increased incorporation of free fatty acids (FFA) into triglyceride—i.e the triglyceride FFA cycle In either case breakdown of ATP occurs and protons are liberated An increased tissue pCO resulting from partial oxidative metabolism can together with protons formed from ATP breakdown cause an intracellular acidosis If mild the acidosis may protect from ischemia by calcium antagonism but if severe increased ischemic damage may result by (1) inhibition of glycolysis and decreased calcium entry (2) acidosis-caused vasospasm (3) inhibition of mitochondrial respiration by NADH and (4) lysosomal activation

can be achieved by low concentrations of acyl carnitine which also accumulates in ischemia These membrane effects may together with early loss of ATP explain the rapid potassium loss after coronary ligation

Loss of *potassium* and gain of *sodium* can be detected within minutes of coronary ligation by coronary venous changes but significant tissue depletion of potassium takes hours to develop Associated with sodium retention is edema formation recently stressed as a cause of the no reflow phenomenon whereby increased swelling of myocardial cells can impinge on the vascular bed and diminish blood flow even if reperfusion were achieved by release of coronary occlusion

A further working hypothesis is that ATP is required for the activity of those ionic pumps which maintain the cellular balance of *calcium ions* Calcium accumulates in cells damaged by ischemia especially after reperfusion The uptake of calcium by mitochondria is energy wasting and must be occurring in the prenecrotic phase

20 and 40 minutes From these points of view, it is of interest that 6 hours post ligation the central infarct zone has an ATP value of below 1 μmoles/g with severe depletion of total adenine nucleotide and of glycogen, but the infarct edge has values of 1 20 to 1 8 μmoles/g and the peri infarct zone has values of 2 to 3 μmoles/g [64] and the glycogen is near normal These indirect arguments suggest that by 6 hours only the peri infarct tissue and perhaps some of the infarct edge is potentially salvable Other information shows[1 7] that 1 to 4 hours after acute coronary ligation in dogs, epicardial ATP even in the central infarct zone is still dropping to the critical levels Four hours post ligation the endocardial zone has developed changes in the K /Na ratio compatible with necrosis with the appearance of mitochondrial dense bodies whereas the epicardial zone has much milder changes and still constitutes a border zone [1 8]

Although indirect evidence links the severity of ATP depletion to irreversibility major reservations are (1) in some situations it is loss of production of glycolytic ATP and not the severity of over all cellular ATP depletion that can be related to the severity of ischemic injury[97 1 9] (2) ATP depletion may merely be a nonspecific index of cell damage and other cellular events[1 9] such as glycogen depletion or potassium sodium changes or activation of lysosomal enzymes[117] can also be circumstantially linked to the onset of necrosis Thus the severity of ATP depletion *should be viewed only as an index of the severity* of ischemic damage The very complex events surrounding the onset of necrosis remain imperfectly understood

Taking into account the evidence based on rates of ATP depletion [7] ionic changes [0 10 1 5] glycogen depletion [1 9] mitochondrial calcium uptake lysosomal activation (see references to Figs 5 and 6) the commencement and pattern of cardiospecific enzyme release [29 3 1 9b] and the rate of onset of Q wave formation [6 6] it is reasonable to conclude that (1) *early irreversible damage* starts about 20 to 40 minutes after complete coronary occlusion in animals and within 2 hours of the onset of symptoms in patients (2) *irreversibility progresses* over a period of several hours as judged by the rate of progression of cellular metabolic changes and enzyme release and Q wave format[illegible] and (3) there is therefore a perceptible pe[illegible]d of several hours duration during which *therapeutic intervention* can be attempted

Basic considerations conclusions

Factors concerned with the initiation of ischemic injury and the progression of such injury to infarction are (1) vascular factors including the role of the controversial thrombus (?) hemodynamic factors *including the hypothesis that* there is a balance between the oxygen supply and demand in the ischemic zone and (3) catecholamine activity, which is generally harmful to the developing infarct, although there are important dose effects and complexities introduced by the relative effects of α and β stimulation The cellular events concerned with the change from ischemia to infarction include ATP depletion, accumulation of fatty acid and acyl CoA alterations in ions including calcium the retention of metabolites (protons carbon dioxide and lactate) and lysosomal activation

There is an important difference between *ischemia* a reversible event and *necrosis* or infarction which is irreversible Experimentally a decreased blood supply or increased hemodynamically induced oxygen demand or increased catecholamine activity can worsen the severity of the ischemic process and the extent of the ultimate infarction However the difficulty in assessing infarct size even in experimental preparations has led to the use of indirect indices of necrosis (ECG changes tissue enzyme *depletion) The existence of a border zone and of cells of interme*diate metabolic characteristics (neither totally healthy nor dead) for anti infarct agents to act on seems probable but by no means proven A general metabolic response further alters the metabolic patterns in the ischemic zones

A consideration of the time scale involved suggest that therapeutic intervention could be justified for at least some hours post coronary ligation or after the onset of symptoms [illegible] patients However in most severely ischemic zones irreversibility would already have set in by 20 to 40 minutes after complete coronary occlusion

REFERENCES

1 Maroko P R Kjekshus J K Sobel B E Watanabe T Covell J W, Ross J Jr and Braunwald E Factors influencing infarct size following experimental coronary artery occlu ions, Circulation 43 67 19[illegible]
2 Hillis L D and Braunwald E Myocardial ischemia N Engl J Med. 296 9 1 1034 1977

an effect on wound healing suggests that membrane stabilization will eventually be tested clinically

Role of general metabolic response in acute myocardial infarction (Fig 7)

In addition to the above events (chiefly described in experimental animals) there is in patients the development of a general metabolic response associated with acute myocardial infarction[1,2] The major components are glucose intolerance[123] increased catecholamine secretion and raised blood free fatty acids Each of these changes could contribute to the progression of ischemic damage (Fig 7) and the catecholamine and fatty acid changes could contribute to the development of arrhythmias (see Opie[7])

Time scale for irreversibility

When does irreversibility set in? Data based on the response to reperfusion after coronary ligation or global ischemia are not necessarily reliable because (1) reperfusion hastens the development of ischemic damage[5] and (2) ischemic damage has a graded and not a global effect depending on the extent of the collateral flow Thus the point of no return must be defined for regional ischemia without reperfusion From the metabolic point of view the changes that have been emphasized in this review are the transition from ischemia to infarction with a fall of ATP increased fatty acid metabolites and the accumulation of lactate protons and CO_2 with a severe intracellular acidosis (Fig 5) with further limitation of flow from edema formation and Ca^{2} contractures Limited information is available about the time scale of such changes in experimental myocardial infarction Over the period 1 to 6 hours post ligation lactate no longer rises (probably because of continued washout by collateral flow) and the pH change is slight but there is progressive depletion of ATP[6] not so much in the central zone but in the border zones[6] Substantial accumulation of fatty acid metabolites probably occurs within one hour[83] Of the major metabolic changes it may be progressive depletion of adenosine triphosphate that becomes critical

On theoretical grounds Kubler and Spieckermann[176] proposed that when the ATP decreases to 2 μM/g (33% of control) no recovery from severe global ischemia can occur Jennings and co workers[27] find that in severely ischemic posterior papillary muscle preparations in which collateral blood flow is less than 10% of control the critical ATP is about 20% of normal—i e about 1.2 μM/g and the critical survival time is between

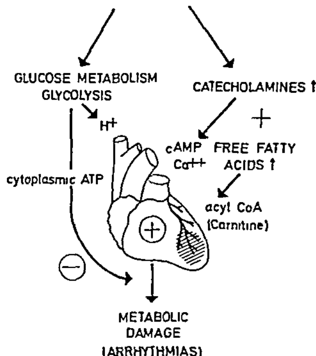


Fig 7 Schematic representation of effects of general metabolic response in acute myocardial infarction on the severity of metabolic damage and the development of arrhythmias. The general metabolic response includes glucose tolerance increased catecholamines and high blood free fatty acids These general metabolic changes can increase metabolic damage (indicated by + sign) and possibly help provoke arrhythmias Catecholamines may exert an effect at a cellular level by cyclic AMP calcium changes and by mobilizing free fatty acids (see *Fig 4*) Free fatty acids may act by intracellular accumulation of acyl CoA carnitine has an important role in the transport of acyl CoA into mitochondria[25] Increased glycolysis can be induced therapeutically by administration of glucose and insulin In severely ischemic tissue protons (H) accumulate and are derived from ATP produced by glycolytic flux Protons do not accumulate to the same extent in moderately ischemic cells because the predominant pattern of metabolism is still oxidative[84] In moderate ischemia increased production of cytoplasmic ATP by promotion of glycolysis may speculatively inhibit the extent of metabolic damage Several agents promoting metabolic damage may also in specified conditions provoke arrhythmias and some antiarrhythmic agents may lessen the extent of ischemic damage (see *Section 2 of this report*) (Based on Bricknell and Opie[9] by permission of the University Park Press)

37 Jennings R B Myocardial ischaemia—observations definitions and speculations, J Molec Cell. Cardiol 1 345 1970
38 Armstrong A Duncan B Oliver M F., Julian D G Donald, K. W Fulton M Lutz W and Morrison, S L. Natural history of acute coronary heart attacks A community study Br Heart J 34 67 1972
39 Oliver M F Significance of ventricular arrhythmias during myocardial ischemia Circulation 53 (Suppl.1) 155 1976
40 Isen, L. T., Humphrey S B and Siner E J Prehospital bradyasystolic cardiac arrest Ann Intern Med. 88 741 1978
41 Moore S Platelet aggregation secondary to coronary obstruction, Circulation 53(Suppl.1) 66 1976
42 Oliva P B and Breckenridge J C Arteriographic evidence of coronary arterial spasm in acute myocardial infarction Circulation 56 366 1977
43 Chandler A. B., Chapman I Erhardt L. R., Roberts W C Schwartz C J Sinapius, D Spain D M Sherry S., Ness P M and Simon T L. Coronary thrombosis in myocardial infarction. Report of a workshop on the role of coronary thrombosis in the pathogenesis of acute myocardial infarction Am J Cardiol. 34 823 1974
44 Maseri, A. L'Abbate A., Pesola A Ballestra, A M Marzilli, M., Maltinti, G Severi, S De Nes D M Parodi, O., and Biagini, A Coronary vasospasm in angina pectoris Lancet 1 713 1977
45 Maseri, A. Severi, S De Nes M L'Abbate A Chierchia S Marzilli, M., Ballestra A M., Parodi, O Biagini, A., and Distante A "Variant angina one aspect of a continuous spectrum of vasospastic myocardial ischemia. Pathogenetic mechanisms estimated incidence clinical and coronarographic findings in 138 patients Am J Cardiol. 42 1019 1978
46 Grayson J., Irvine M., Parratt J R. and Cunningham J Vasospastic elements in myocardial infarction following coronary occlusion in the dog Cardiovasc Res. 2 54 1968
47 Gregg D E Coronary circulation in health and disease Philadelphia 1950 Lea & Febiger
48 Weisse A. B Senft A., Khan M I., and Regan T J Effect of nitrate infusions on the systemic and coronary circulations following acute experimental myocardial infarction in the intact dog Am J Cardiol. 30 362 1972
49 Capurro N L Kent, K M., and Epstein S E Comparison of nitroglycerin nitroprusside and phentolamine induced changes in coronary collateral function in dogs J Clin Invest 60 295 1977
50 Capurro N L Kent K M Smith, H J Aamodt R and Epstein, S E Acute coronary occlusion prolonged increase in collateral flow following brief administration of nitroglycerin and methoxamine Am J Cardiol 39 679 1977
51 Gold, H K Leinbach R C and Maroko P R. Propranolol induced reduction of signs of ischemic injury during acute myocardial infarction, Am J Cardiol 38 689 1976
52 Paroldi G and Scomazzoni, G Coronary circulation of th n rmal and pathologic human heart Armed For e In titute of Pathology 1967 Washington D C
53 Cohn I H Report of Round Table Discussion Acute surg i i tervention in Kaindl E., Pachinger O., and Probst editors The first 24 hours in myocardial infarction Baden Baden 1977 Verlag Gerhard Witzstrock, pp 209 213
54 Jennings, R B Sommers H M Smyth, G A, Flack H A., and Linn, H Myocardial necrosis induced by temporary occlusion of a coronary artery in the dog Arch. Pathol 70 68 1960
55 Shen A. C., and Jennings R. B Myocardial calcium and magnesium in acute ischemic injury Am. J Pathol 67 417 1972
56 Jennings, R. B and Ganote C E Mitochondrial structure and function in acute myocardial ischemic injury Circ Res 38(Suppl 1) 80 19 6
57 Hutchins G M. and Bulkley B H Correlation of myocardial contraction band necrosis and vascular patency A study of coronary artery bypass graft anastomoses at branch points, Lab Invest. 36 6.. 1977
58 Braunwald E Control of myocardial oxygen consumption Physiologic and clinical considerations, Am J Cardiol 27 416 1971
59 Wollenberger A Relation between work and labile phosphate contents in the isolated dog heart, Circ Res 5 175 1957
60 Opie L H and Owen P Effect of glucose-insulin-potassium infusions on arteriovenous differences of glucose and of free fatty acids and on tissue metabolic changes in dogs with developing myocardial infarction Am. J Cardiol 38 310 1976
61 Hearse D J Opie L. H Katzeff I E Lubbe W F van der Werff T J Peisach, M and Boule G Characterization of the "border zone" in acute regional ischemia in the dog Am. J Cardiol. 40 716 1977
62 Puri, P S Modification of experimental myocardial infarct size by cardiac drugs, Am. J Cardiol. 33 5.. 1974
63 Hood W B., Jr Covelli, V H Abelmann W H and Norman J C Persistence of contractile behaviour in acutely ischaemic myocardium Cardiovasc. Res. 3 ... 1969
64 Opie L. H. Effects of regional ischemia on metabolism of glucose and fatty acids Relative rates of aerobic and anaerobic energy production during myocardial infarction and comparison with effects of anoxia Circ Res 38(Suppl.1) 52 1976
65 Regan T J Harman M A., Lehan P H Burke W M and Oldewurtel H A Ventricular arrhythmias and potassium transfer during myocardial ischemia and intervention with procaine amide insulin, or glucose solution J Clin Invest 46 1657 1967
66 Becker L. C Ferreira R., and Thomas, M Effect of propranolol and isoprenaline on regional left ventricular blood flow in experimental myocardial ischaemia Cardiovasc Res 9 1 8 1975
67 Lubbe W F., Peisach, M Pretorius R., Bruyneel, K J and Opie L H Distribution of myocardial blood flow before and after coronary artery ligation in the baboon Relation to early ventricular fibrillation Cardiovasc Res 8 4 8 1974
68 Chance B Border zone (Discussion) Circ Res 38(Suppl 1) 69 1976
69 Steenbergen C., DeLeeuw G Barlow C Chance B, and Williamson J R Heterogeneity of the hypoxic state in perfused rat heart Circ Res 41 606 1977
70 Hirzel, H O Sonnenblick, E. H and Kirk, E S Absence of a lateral border zone of intermediate creatine phosphokinase depletion surrounding a central infarct 24 hours after acute coronary occlusion in the dog Circ. Res. 41 673 1977
71 Raab W van Lith, P Lepeschkin E and Herrlich, H C. Catecholamine-induced myocardial hypoxia in the presence of impaired coronary dilatability independent

3 Surawicz B The disputed S T egment mappin^ is the technique ready for wide application in practice? Am J Cardiol 40 13, 19,7
4 Cox J L McLaughlin V W Flowers N C and Horan L G The ischemic zone surrounding acute myocardial infarction Its morphology as detected by dehydrogenase staining AM HEART J 76 650 1968
5 Salimi A Oliver G C Lee J and Sherman L A *Continued incorporation of circulating radiolabeled* fibrinogen into preformed coronary artery thrombi Circulation 56 213 19 7
6 Reid P R Taylor D R Kelly D T Weisf ldt M L Humphries J O'Neal Ross R S and Pitt B Myocardial infarct extension detected by precordial ST segment mapping N Engl J Med 290 123 19,4
7 Mathey D Bleifeld W Buss, H and Hanrath P Creatine kinase release in acute myocardial infarction correlation with clinical electrocardiographic and pathological findings, Br Heart J 37 1161 1975
8 Hutchins G M and Bulkley B H Infarct expansion versus extension two different complications of acute myocardial infarction Am J Cardiol 41 1127 1978
9 Oliver M F Metabolic response during impending myocardial infarction II Clinical implications Circulation 45 491 19,2
10 Wartman W B Definition of myocardial infarct *in* James, T N and Keyes J W editors The etiology of myocardial infarction Boston 1963 Little Brown & Company pp 115 134
11 Baroldi G Acute coronary occlusion as a cause of myocardial infarct and sudden coronary heart death Am J Cardiol 16 859 1965
12 Baroldi G Different types of myocardial necrosis in coronary heart disease a pathophysiological review of their functional significance AM HEART J 89 742 19 5
13 Schlesinger M J and Reiner L Focal myocytolysis of the heart Am J Pathol 31 443 1955
14 Waldenstrom A P Hjalmarson A C and Thornell L T A possible role of noradrenaline in the development of myocardial infarction An experimental study in the isolated rat heart AM HEART J 95 43 1978
15 *Mitchell J R A and Schwartz, C J The relation* between myocardial lesions and coronary artery disease II A selected group of patients with massive cardiac necrosis or scarring Br Heart J 25 1 1963
16 Fulton W F M and Sumner D J Causal role of coronary thrombotic occlusion and myocardial infarction Evidence of stereo angiography serial sections and I fibrinogen autoradiography (Abstract) Am J Cardiol 39 322 1977
17 Ridolfi, R L and Hutchins G M The relation hip between coronary artery lesions and myocardial infarcts ulceration of atherosclerotic plaques precipitating coronary thrombosis AM HEART J 93 468 1977
18 Erhardt L R Coronary thrombosis—cause or consequence? *in* Kaindl F Pachinger O and Probst P editors The first 24 hours in myocardial infarction Baden Baden 1977 Verlag Gerhard Witzstrock pp 6-10
19 Roberts W C Coronary thrombosis and fatal myocardial infarction Circulation 49 1 1974
20 Muller J E Maroko P R and Braunwald E Evaluation of precordial electrocardiographic mapping as a means of assessing chan es *in myocardial* ischemic injury Circulation 52 16 19 5
21 Luxton M R Russell D C Murray A Williamson D Neilson J M M and Oliver M F Praecordial ST segment elevation New technique for continuous recording and analysis Br Heart J 39 493 1977
22 Holland R P and Brooks H TQ ST segment mapping critical review and analysis of current concepts Am J Cardiol 40 110 1977
23 Norris R N Barratt Boyes C Heng M K and Singh B N Failure of ST segment elevation to predict severity of acute myocardial infarction Br Heart J *38 85 1976*
24 Fixler D E Buja L M Wheeler J M and Willerson J T Influence of mannitol on maintaining coronary flows and salvaging myocardium during ventriculatomy and during prolonged coronary artery ligation Circulation 56 340 197,
25 Hillis D L Askenazi J Braunwald E Radvany P Muller J E Fishbein M C and Maroko P Use of changes in the epicardial QRS complex to assess interventions which modify the extent of myocardial necrosis following coronary artery occlusion Circulation 54 591 1976
26 Selwyn A P and Shillingford J P Praecordial mapping of Q waves and RS ratio changes in acute myocardial infarction Cardiovasc Res 11 167 19,7
26a Selwyn A Ogunro E and Shillingford J P The loss of electrically active myocardium in cardiogenic shock Eur J Cardiol 6 337 1978
27 Awan N A Miller R R Vera Z Janzen D A Amsterdam E A and Mason D T Noninvasive assessment of cardiac function and ventricular dyssynergy by precordial Q wave mappin^ in anterior myocardial infarction Circulation 55 833 1977
28 Askenazi J Maroko P Lesch M, and Braunwald E Usefulness of ST segment elevations as predictors of electrocardiographic signs of necrosis in patients with acute myocardial infarction Br Heart J 39 764 1977
29 Sobel B E Bresnahan G F Shell, W E, and Yoder R D Estimation of infarct size in man and its relation to prognosis Circulation 46 640 1972
30 Norris R M Whitlock R M L Barratt Boyes, C and Small C W Clinical measurement of myocardial infarct size Modification of a method for the estima*tion of total creatine phosphokinase release after myo*cardial infarction Circulation 51 614 19,5
31 Sobel, B E Markham J and Roberts R Factors influencing enzymatic estimates of infarct size Am J Cardiol 39 130 1977
32 Shell W E and Sobel B E Protection of jeopardized ischemic myocardium by reduction of ventricular after load N Engl J Med 291 481 1974
33 Varonkov Y Shell W E Smirnov V Gukovsky D and Chazov E Augmentation of serum CPK activity by digitalis in patients with acute myocardial infarction Circulation 55 719 1977
34 Roberts, A J Cipriano P R Alonso D R Jacobstein J G Combes J R and Gay W A Jr Evaluation of methods for the quantification of experimental myocardial infarction Circulation 57 35 1978
35 Wackers, F J Th Becker A E Samson G Sokok E B, van der Schoot J B Vet A J Th Lie K I Durrer D and Wellens H Location and size of acute transmural myocardial infarction estimated from thallium 201 scintiscans Circulation 56 72 1978
36 Sobel B E, Weiss E J Welch M J Siegel B A, and Ter Pogossian *Detection of remote myocardial infarc*tion in patients with positron transaxial tomography and intravenous C palmitate Circulation 55 853 1977

107 Bruno F P., Cobb F R Rivas F and Goodrich J K. Evaluation of 99m technetium stannous pyrophosphate as an imaging agent in acute myocardial infarction Circulation 54 71 1976
108 Buja L. M Parkey R W., Dees, J H Stokely E M., Harris, R A. Jr Bonte F J., and Willerson J T Morphologic correlates of technetium 99m stannous pyrophosphate imaging of acute myocardial infarcts in dogs Circulation 52 596 1975
109 Marcus, M. L., Tomanek, R J Ehrhardt J C Kerber R E., Brown, D B and Abboud F M Relationships between myocardial perfusion myocardial necrosis and technetium 99m pyrophosphate uptake in dogs subjected to sudden coronary occlusion Circulation 54 647 1976
110 Smith, H J Singh, B N Nisbet H D., and Norris R M Effects of verapamil on infarct size following experimental coronary occlusion Cardiovasc Res 9 569 1975
111 Wolf R Habel F., Wit E Notges A Everling F and Hochrein H Effect of verapamil on hemodynamics and size of acute myocardial infarction (in German) Herz 2 110 1977
112 Poole Wilson P A Is early decline of cardiac function in ischaemia due to carbon dioxide retention? Lancet 2 1285 1975
113 Williamson J R., Woodrow M L. and Scarpa A Calcium binding to cardiac sarcolemma *in* Fleckenstein, A., and Dhalla N S., editors Recent advances in studies on cardiac structure and metabolism Baltimore, 1975 University Park Press pp 61 71
114 Rovetto M J Lamberton W F., and Neely J R Mechanisms of glycolytic inhibition in ischemic rat hearts, Circ Res. 37 742 1975
115 Armiger L. C., Garin J B and Herdson P B Mitochondrial changes in dog myocardium induced by neutral lactate in vivo Lab Invest 31 29 1974
116 Wissner S B The effect of excess lactate upon the excitability of the sheep Purkinje fiber J Electrocardiol 7 17 1974
117 Ravens K. G., and Gudbjarnason, S Changes in the activities of lysosomal enzymes in infarcted canine heart muscle Circ Res 24 851 1969
118 Wildenthal, K Lysosomal alterations in ischemic myocardium result or cause of myocellular damage? J Molec Cell Cardiol. 10 595 1978
119 Spath, J A Jr Lane D L and Lefer A M Protective action of methyl prednisolone on the myocardium during experimental myocardial ischemia in the cat Circ Res 35 44 1974
120 Welman E and Peters T J Enhanced lysosome fragility in the anoxic perfused guinea pig heart e[illegible] of glucose and mannitol J Molec Cell. Cardi[illegible] 1977
121 Nayler W G Yepez C., Gran, A and Slade [illegible] Protective effect of methylprednisolone sodium succinate on the ultrastructure and resting tension of hypoxic heart muscle Cardiovasc Res 12 91 [illegible]
122 Opie L. H The metabolic response in acute myocardial infarction, Br Heart J 33 129 1971
123 Sowton E Cardiac infarction and the glucose tolerance test Br Med J 1 84 1962
124 Valori, C Thomas M and Shillingford J Free noradrenaline and adrenaline excretion in relation to *clinical syndromes following myocardial infarction* Am J Cardiol 20 605 1967
125 Oliver M F., Kurien V A and Greenwood T W Relation between serum free fatty acid and arrhythmias and death after acute myocardial infarction Lancet 1 710 1968
126 Kubler W., and Spieckermann, P G Regulation of glycolysis in the ischaemic and anoxic myocardium J Molec Cell. Cardiol 1 351 1970
127 Jennings R B Hawkins H K., Lowe J E Hill, M L. Klotman S and Reimer K. A Relation between high energy phosphate and lethal injury in myocardial ischemia in the dog Am J Pathol 92 18 1978
127a Allison T B Ramey C A and Holsinger J W Jr Transmural gradients of left ventricular tissue metabolites after circumflex artery ligation in dogs J Molec Cell Cardiol 9 837 1977
128 Banka, V S Bodenheimer M M Ramanathan K B Hermann G A. and Helfant R H Progressive transmural electrocardiographic myocardial potassium sodium ratio and ultrastructural changes as a function of time after acute coronary occlusion Am J Cardiol 42 429 1978
129 Bricknell O L and Opie L. H Effects of substrates on tissue metabolic changes in the isolated rat heart during underperfusion and on release of lactate dehydrogenase and arrhythmias during reperfusion Circ Res 43 102 1978
129a Rose A Opie L H and Bricknell, O. Evaluation of histologic criteria of early experimental myocardial infarction Comparison with biochemical and electrocardiographic parameters Arch Pathol. 100 5[illegible] 1976
129b Ahmed, S A., Williamson J R Roberts, R Clark F E., and Sobel B E The association of increased plasma MB CPK activity and irreversible ischemic myocardial injury in the dog Circulation 54 1[illegible] 1976

of external cardiac work Am J Cardiol 9 4ɔɔ 1962
72 Opie L. H Metabolism of free fatty acids glucose and catecholamines in acute myocardial infarction Relation to myocardial ischemia and infarct size Am J Cardiol 36 938 1975
73 Regan T J, Markov A Oldewurtel H A and Burke W M Myocardial metabolism and function during ischaemia response to L-noradrenaline Cardiovasc Res 4 334 1970
74 Shell, W E and Sobel B E Deleterious effects of increased heart rate on infarct size in the conscious dog Am J Cardiol 31 474 1973
75 Redwood D R Smith F R and Epstein S E Coronary artery occlusion in the conscious dog Effects of alterations in heart rate and arterial pressure on the degree of myocardial ischemia Circulation 46 323 1972
76 Mjøs O D Kjekshus J K and Lekven J Importance of free fatty acids as a determinant of myocardial oxygen consumption and myocardial ischemic injury during norepinephrine infusions in dogs J Clin Invest 53 1290 1974
77 Reuter H Localization of β adrenergic receptors and effects of noradrenaline and cyclic nucleotides on action potentials ionic currents and tension in mammalian cardiac muscle J Physiol 242 429 1974
78 Evans C L The mechanism of cardiac acceleration by warmth and by adrenaline J Physiol 51 91 1917
79 Lehninger A L Mitochondria and calcium transport Biochem J 119 129 1970
80 Harris P A theory concerning the course of events in angina and myocardial infarction Eur J Cardiol 3 157 1975
81 Scheuer J and Brachfeld N Myocardial uptake and fractional distribution of palmitate 1 C by the ischemic dog heart Metabolism 15 945 1966
82 Gevers, W Generation of protons by metabolic processes in heart cell J Molec Cell Cardiol 9 867 1977
83 Shug A L Shrago E Bittar N Folts J D and Kokes J R Long chain fatty acyl CoA inhibition of adenine nucleotide translocase in the ischemic myocardium Am. J Physiol 228 689 1975
84 Rona G Huttner I and Boutet M Microcirculatory changes in the myocardium with particular reference to catecholamine induced cardiac muscle cell injury *in* Messen H editor Handbuch der allgemeinen Pathologie III/7 Microcirculation Berlin 1977 Springer Verlag
85 Fleckenstein A Specific inhibitors and promoters of calcium action in the excitation-contraction coupling of heart muscle and their role in the prevention or production of myocardial lesions *in* Harris P Opie L H editors Calcium and the heart London 1971 Academic Press
86 Mjøs O D Effect of inhibition of lipolysis on myocardial oxygen consumption in the presence of isoproterenol J Clin Invest 50 1869 1971
87 Kjekshus, J Effects of lipolytic and inotropic stimulation on myocardial ischemic injury Acta Med Scand Suppl. 587 35 1976
88 Lekven J and Semb G Effect of dopamine and of calcium on lipolysis and on myocardial ischemic injury following acute coronary artery occlusion in the dog Circ Res. 34 349 1974
89 Simonsen S and Kjekshus J K The effect of free fatty acids on myocardial oxygen consumption during atrial pacing and catecholamine infusion in man Circulation 58 485 1978
90 Vetter N J Strange R C Adams W and Oliver M F Initial metabolic and hormonal response to acute myocardial infarction Lancet 1 284 1974
91 Staszewska Barczak J The reflex stimulation of catecholamine secretion during the acute stage of myocardial infarction in the dog Clin Sci. 41 419 1971
92 Videbaek, J Christensen N J., and Sterndorff B Serial determinations of plasma catecholamines in myocardial infarction Circulation 46 846 1972
93 Herbaczynska Cedro K The influence of adrenaline secretion on the enzymes in heart muscle after acute coronary occlusion in dogs Cardiovasc Res 4 168 1970
94 Rona G Chappel C I Balazs T and Gaundry R An infarct like myocardial lesion and other toxic manifestations produced by isoproterenol in the rat Arch Pathol 67 443 1959
95 Gebhard M M Denkhaus H Saki K and Spieckermann P G Energy metabolism and enzyme release J Molec Med 2 291 1977
96 Font B Vial C and Goldschmidt D Enzyme levels and metabolite release in the ischaemic myocardium J Molec Med 2 291 1977
97 Bricknell O L and Opie L H Glycolytic ATP and its production during ischaemia in isolated Langendorff perfused rat hearts *in* Kobayashi, T Sano T and Dhalla N S editors Recent advances in studies on cardiac structure and metabolism Vol. 11 Baltimore 1978 University Park Press pp 509-519
98 McDonald T F Hunter E G and MacLeod D P Adenosine triphosphate partition in cardiac muscle with respect to transmembrane electrical activity Pflug Arch 322 95 1971
99 de Leiris J Opie L. H., and Lubbe W F Effects of free fatty and glucose on enzyme release in experimental myocardial infarction Nature 253 46 1975
100 Neely J R Whitmer J T and Rovetto M J Effect of coronary blood flow on glycolytic flux and intracellular pH in isolated rat hearts Circ Res 37 33 1975
101 Weishaar R Sarma J S M Maruyama Y Fischer R and Bing R J Regional blood flow contractility and metabolism in early myocardial infarction Cardiology 62 2 1977
102 Wood J M Bush B Pitts B J R and Schwartz A Inhibition of bovine heart Na K ATPase by palmityl carnitine and palmityl CoA Biochem Biophys Res Comm 74 677 1977
102a Sobel B E Corr P B Robison A K Goldstein R A Witkowski, F X and Klein M S Accumulation of lysophosphoglycerides with arrhythmogenic properties in ischemic myocardium J Clin Invest 62 546 1978
103 Thomas M Shulman G and Opie I Arteriovenous potassium changes and ventricular arrhythmias after coronary artery occlusion Cardiovasc Res 4 327 1970
104 Jennings, R B Crout J R and Smetters G W Studies on the localization of potassium in the early myocardial ischemic injury Arch Pathol 63 586 1957
105 Willerson J T Watson J T., Hutton I Templeton G H and Fixler D E Reduced myocardial reflow and increased coronary vascular resistance following prolonged myocardial ischemia in the dog Circ Res 36 771 1975
106 Burton K P Hagler H K Templeton, G H., Willerson J T and Buja L. M Lanthanum probe studies of cellular pathophysiology induced by hypoxia in isolated cardiac muscle J Clin. Invest 60 1289 1977

and the late rightward forces do not reach one millivolt in magnitude the likely choice is posterobasal infarction Further caution must be applied in this situation as anterior fascicular delay may be present in the complete absence of coronary disease or infarction

In a very recent study echocardiography proved to be a highly useful discriminant in identifying patients with dilated right ventricles or with hypokinetic posterior left ventricular walls enabling better separation of RVH from posterobasal infarct cases than was possible from vectorcardiographic considerations alone[9]

Left ventricular hypertrophy and pseudo infarction

The posterior QRS addition to QRS voltage which occurs in left ventricular hypertrophy may mimic anterior myocardial infarction[117, 145, 158] Early posterior addition may reduce the duration and magnitude of the normal early anterior forces to very low values or to zero In addition advanced LVH as described previously, may in its most advanced form result in a clockwise horizontal loop[41, 49] Thus the picture of extensive anterior infarction may be closely mimicked Several authors have studied this problem and all agree that the usual diagnostic criteria for anterior infarction are much less sensitive in the presence of left ventricular hypertrophy especially when this is the result of aortic valve disease[1, 145, 15] Therefore when the vectorcardiographer reviews a horizontal QRS loop lacking anterior forces and presenting with marked posterior orientation and even with clockwise rotation he should suspect a pseudo infarction if the QRS voltage is high suggesting concomitant left ventricular hypertrophy

Unfortunately neither the direction nor the rotational characteristics of the T loops in these cases serve as a useful discriminant between severe left ventricular hypertrophy and LVH accompanied by anterior infarction[06, 2]

Uncommonly the frontal loop in severe left ventricular hypertrophy may mimic inferior myocardial infarction with an upward bowing of the first half of the QRS loop which may remain superior for 30 msec thus mimicking a diaphragmatic infar[illegible] These loops are probably somewhat more c[illegible] when the left ventricular hypertroph[illegible] basis of aortic insufficiency than aortic [illegible] although both lesions may

result in a pseudo inferior infarction picture

Cardiomyopathies of various etiologies may mimic myocardial infarction vectorcardiographically[140, 142, 143, 1, 5, 151] The markedly hypertrophied intraventricular septum seen in hypertrophic subaortic stenosis is believed to be responsible for the marked initial rightward anterior forces which may occur in that condition and which may mimic dorsal or lateral infarction

However at least one study denies that any significant difference exists between the left ventricular hypertrophy patterns resulting from aortic stenosis aortic insufficiency or hypertrophic cardiomyopathy[41]

Certainly the myocardial deposits or scarring which occur in infiltrative cardiomyopathies such *as sarcoidosis or amyloid disease* may result in QRS loop deformities and bites which are indistinguishable from those seen in coronary disease and myocardial infarction[11, 1, 1, 11, 11]

The congestive cardiomyopathies may present with a wide variety of vectorcardiographic abnormalities particularly conduction disorders including hemiblocks and simple axis shifts[1] However in many such cases mimicry of myocardial infarction in any location occurs

In cardiomyopathies the combination of conduction disturbance small areas of fibrosis and ventricular hypertrophy can readily lead to distortions of the activation sequence leading to QRS loop deformities readily mistaken for those of myocardial infarction An interesting variant is seen in the mitral valve prolapse syndrome in which coronary disease is absent but myocardial contractile abnormality is frequently present Although the QRS loops in these patients are commonly normal an occasional patient will present with complete absence of anterior forces resembling anterior myocardial infarction

Another variety of cardiomyopathy which presents a rather typical pseudo infarction pattern is Duchenne s muscular dystrophy in which pathological changes occur in the posterobasal wall of the left ventricle[50] As might be expected this results in an anterior displacement of the QRS loop which thus could be misinterpreted as true posterior infarction

The pre excitation (WPW) syndrome in which initial QRS activation may be directed markedly anterior posterior or superior and thus may mimic anterior posterior or inferior infarction will be discussed in a separate section

Fundamentals of clinical cardiology

Clinical vectorcardiography in adults Part 2

Irwin Hoffman M D
New Hyde Park and Far Rockaway N Y

Pulmonary emphysema and pseudo anterior infarction

The effects of emphysema on the distribution of QRS forces on the torso surface has been mentioned previously in this review The resultant decrease in anterior QRS forces which may be simulated by experimental overinflation of the lungs may result in a scalar ECG and a vectorcardiogram resembling anterior myocardial infarction owing to the poor progression of scalar precordial R waves and the minute duration and magnitude of anterior forces recorded Watanabe and associates have studied this problem using computer techniques and multivariate statistical analysis Four vectorcardiographic measurements were selected to enable the best discrimination between these two conditions The location of the 15 msec vector in Lead Z (anterior or posterior) was one useful criterion The mean value for anterior duration was 30 msec in the emphysema group but only 14 msec in the anterior infarction group The authors found that 25 msec provided a good discriminating point The second criterion used was the ratio of the rightward forces (Sx) divided by the sum of the leftward plus rightward forces (Rx + Sx) This value was 0 417 in the chronic obstructive lung disease group and 0 245 in the anterior infarction group—indicating a greater relative strength of rightward voltage in the emphysema patients

The third criterion which separates the groups was the simple voltage summation of Rx + Rx (leftwards plus posterior forces) This value was 0 85 in the emphysema group but 1 6 in the anterior infarction group Finally the total QRS duration was a fourth useful discriminator with a mean value of 93 msec in the emphysema group and 105 msec in the myocardial infarction group Despite the use of these criteria the greatest difficulties are encountered in patients with emphysema whose anterior forces are completely absent This may occur although infrequently in the absence of coronary disease or myocardial infarction and it poses a sometimes impossible differential diagnosis

Although considerable overlap was encountered by all investigators who have approached this problem it seems apparent that the use of multiple criteria rather than any single one is best in attempting to separate the two conditions Mitral stenosis which often results in a small posteriorly oriented QRS loop with terminal forces oriented to the right may also present difficulties in discrimination against anterior infarction Fortunately clinical features and the age and sex of the patients are frequently very valuable in making a preliminary differentiation in mitral stenosis whereas the patients with chronic obstructive lung disease are often clinically very like patients with anterior infarction

Pseudo infarction with right ventricular hypertrophy

Since right ventricular hypertrophy adds both anterior and rightward QRS forces the pseudo infarction frequently diagnosed is posterior lateral in location The differential diagnosis between right ventricular hypertrophy and posterobasal infarction has been presented by several authors If the major QRS axis is in the left anterior quadrant of the horizontal plane

From the Department of Cardiology Long Island Jewish Hillside Medical Center New Hyde Park N Y and the Department of Cardiology South Shore Division St John's Episcopal Hospital Far Rockaway N Y

Received for publication March 14 1979

Reprint requests Irwin Hoffman M D Long Island Cardiovascular Group P C [illegible] Ceda hurst N Y 11516

0002-8703/80/090373 + [illegible] © 1980 The C V Mosby Co

that this may occur in subjects free of right ventricular hypertrophy or posterior myocardial infarction

Superior and inferior divisional blocks (references 2 to 16 173 to 188)

Rosenbaum s concept of the trifascicular ventricular conduction system *consisting of the right* bundle branch and a left branch *composed of two* divisions has received a wide acceptance as has his terminology for conduction disorders in the divisions of the left bundle as anterior and posterior hemiblock[173] The characteristic electrocardiographic and vectorcardiographic alterations induced by poor conduction in the divisions of the left bundle have been reproduced by intracoronary injections[17 177 178] and by *surgical* interruption in animals and in humans *intermittent* conduction disorders have been observed in some subjects[177 1 0] Rosenbaum s contribution to the understanding of ventricular conduction disorders is *extremely important* However, two aspects of his conception and terminology probably require *refinement* All the diagnostic features which will be described for fascicular blocks are derived from the frontal *reference* plane, owing to *changes* in the Y axis[174] *Very simply* stated a markedly *superior* shift in the frontal plane corresponds to superior divisional block or, in Rosenbaum s terminology *left anterior* hemiblock On the other hand a markedly inferior *and somewhat rightward shift* occurs with inferior divisional block referred to by Rosenbaum as left posterior hemiblock[173] Since neither the anterior or *posterior* directions are reflected in the *frontal reference* plane the *terms* anterior and posterior to describe these changes are probably inappropriate and should be replaced by superior and inferior

Anatomical studies in recent years have confirmed that the left bundle branch ramifies more extensively than previously thought with a third or anterior fascicle commonly present Obviously the *term* hemiblock does not properly fit a trifascicular *division* of the left bundle branch[95] Instead of hemiblock the term divisional *block* seems more appropriate as it allows characterization of [illegible]nduction disorders in the third or anterior f[illegible] and even leaves room for future anato[illegible] dis[illegible]ries

For these r[illegible] [illegible]he portions of this review dealing with d[illegible] [illegible]locks of the left bundle the terms sup[illegible] [illegible]ional block and inferior divisional block will be used rather tha[illegible] the more commonly accepted *hemiblocks*

Readers are reminded that for decades myocardial infarctions on the diaphragmatic surface of the left ventricle were referred to as posterior infarcts and that many years of educational activity were necessary before the term inferior infarction was accepted Posterior infarction *has come to mean* infarction of the posterobasal *segment of the left ventricle* and is quite distinct *from* inferior infarction[3 8] Anterior divisional block does exist but it results appropriately in *an anterior* shift of QRS which may be quite distinct *and separate* from a superior axis shift—as discussed in a prior section The typical vectorcardiographic changes of superior or inferior *divisional* block uncomplicated by other pathology, are easy to describe and to understand Excellent descriptions and examples may *be found* in all of the general references given in the first section of this review [8] In superior divisional block the major change is a shift of the major axis of the frontal plane loop to a markedly superior position lying above the X axis and commonly well above The rotation is always counterclockwise The initial forces in uncomplicated superior divisional block are almost invariably directed to the right and inferiorly owing to unopposed activation of the septum from the uninvolved branches of the conducting system resulting in a distinctly more inferior orientation *than is usual for normal* early activation[' 1..]

This markedly inferior and rightward orientation of initial vectors is responsible *for* one of the diagnostic dilemmas occasionally encountered in uncomplicated superior divisional block[..] *This is the appearance of small but distinct* Q waves in the right precordial leads particularly in Leads V_2 and V_3[94] The Q waves result because the initial *forces as described above are oriented* so inferiorly as to register as negative deflections in the precordial lead axes

The horizontal *loop* however exhibits its usual smooth counterclockwise course with the major vectors oriented left and *posterior* as in the *normal case In patients with* intermittent superior divisional block slight prolongation has commonly been observed but never *beyond the upper limits of normal*[...] Terminal "cluttering" of time dashes is sometimes also seen These observations indicate that *the disorder is indeed a conduction* delay

Inferior divisional block produces the expected

Infarction and pseudo infarction after coronary bypass surgery

Between five and 25% of patients undergoing coronary artery bypass surgery develop new Q waves postoperatively commonly attributed to postoperative myocardial infarction Vectorcardiographic study has been performed pre and postoperatively in such patients and a higher recognition rate for infarction has been claimed for the vectorcardiogram[153, 15]

However it should be pointed out that QRS voltage changes may occur as a result of alterations in postoperative hematocrit rather than true cardiac pathology[152] Further when new Q waves are correlated with bypass graft patency and postoperative ventriculograms some patients with new Q waves are found to present with patent grafts to the presumed infarcted area which exhibits normal contractility in contrast ventriculographic study[15] Thus at least some of the new Q waves seen postoperatively may be the result of something other than myocardial infarction—and should be included in the list of causes of pseudo infarction Infrequently pseudo infarction is encountered with hyperkalemia[57] or straight back syndrome[11]

Right bundle branch block (references 2 to 16 161 to 172)

The experimental vectorcardiography of right bundle branch look has been studied in humans—catheter induced in the right ventricle postoperatively (after repairs of ventricular septal defects) and in patients whose conduction disorder was intermittent or was induced by premature atrial stimulation[1, 5, 1]

From these observations it can be reasonably stated that right bundle branch block is essentially a distal disorder of conduction leaving unaffected the initial 40 msec of the QRS complexes Beginning at about 60 msec after the E point the QRS loop deviates anteriorly and to the right with the terminal forces exhibiting clustered time dashes due to slower activation in the right side of the septum and the right ventricle[4, 6] Thus it is evident that in right bundle branch block the QRS loops are prolonged in duration (increased number of time dashes) to values of 110 to 170 msec or even longer

The sparing of initial forces indicates that those diagnoses which depend on alterations in the earlier QRS vectors (such as myocardial infarction and even left ventricular hypertrophy) could still be established in the presence of right bundle branch block

Several authorities have suggested abandonment of the term right bundle branch block in favor of right ventricular conduction delay thus eliminating the unsatisfactory term incomplete right bundle branch block which has been used to describe a similar electrocardiographic and vectorcardiographic picture but with a shorter total time duration than 120 msec In the author s experience right ventricular conduction delays with a total duration of less than 120 msec usually exhibit the terminal slowing right and posterior to the E point while in instances with conduction prolongation to 120 msec or greater terminal delay is more commonly anterior and rightwards

The characteristic horizontal plane QRS loop in right bundle branch block is very easy to recognize The initial portions of the loop are very similar to the normal QRS with counterclockwise movement from the E point beginning in an anterior direction and with the major QRS forces oriented to the left and posterior Instead of returning to the E point however the QRS loop continues and inscribes a large appendage anterior and to the right of the E point usually with counterclockwise rotation in the appendage and with clustering of the time dashes[18, 170]

The frontal QRS loop has a normal axis that is an orientation inferior to the X axis and to the left of the E point The initial portion of the QRS loop may be normal in the frontal plane with either clockwise or counterclockwise rotation but the characteristic feature is the terminal appendage which is always oriented to the right but may be inferior or superior to the E point In uncomplicated right bundle branch block the frontal axis is neither markedly superior nor markedly rightwards as is the case when a left divisional block is superimposed[17, 72]

The horizontal plane T loop in right bundle branch block is characteristically left and posterior with clockwise rotation The T loops in right bundle branch block and its variations will be described in a separate section on T loops Occasionally in the acute and experimental varieties of right bundle branch block described above the body of the QRS loop is inscribed completely anterior to the E point and may even exhibit clockwise rotation[96] It is important to realize

sional block[1, 3] However the frontal plane vectorcardiographic loop is quite characteristic and easy to recognize The initial forces are always superior and may be oriented to the left or right The major axis of the loop is distinctly vertical close to the Y axis and terminal slowing oriented to the right is always present as in uncomplicated right bundle branch block

Various configurations of the QRS loop have been described in the horizontal plane with clockwise counterclockwise and figure of eight loops occurring with about equal frequency In the series of Varriale and Kennedy[198] who reported 12 patients with this combination all the horizontal plane loops initial forces were anterior or directly leftwards The horizontal plane loops present terminal rightward anterior conduction delay with clustering of time dashes characteristic of right bundle branch block. Many horizontal loops of patients with combined right bundle branch block and inferior divisional block have very prominent anterior QRS forces unrelated to the presence of dorsal myocardial infarction or of right ventricular hypertrophy Thus this particular combination of divisional blocks again presents the opportunity for overdiagnosis of prominent anterior QRS forces Five of Kennedy and Varriale s patients had well established inferior infarction in addition to their conduction disorders and in two anterior infarction was also present Before the diagnosis of right bundle branch block combined with inferior divisional block is made four other entities must be considered These are right bundle branch block combined with one of the following right ventricular hypertrophy chronic pulmonary disease slender body build or extensive lateral infarction

Ordinary clinical examination is usually sufficient to rule out the first three of these possibilities and in the last abnormally large and prolonged early rightward forces might suggest the correct diagnosis

Obviously right bundle branch block combined with inferior divisional block produces a marked vertical shift in the frontal plane axis while right bundle branch block combined with superior divisional block produces a marked superior shift in the frontal plane axis In some patients with chronic right bundle branch block the associated inferior or superior divisional block may be intermittent and it was from observations of axis shift in such cases that Rosenbaum first deduced logically the concept of a multidivisional conducting system arising from the left bundle branch

Myocardial infarction combined with superior or inferior divisional block (references 2 to 16 199 to 209)

Inferior myocardial infarction combined with superior divisional block results in a characteristic and easy to recognize frontal vectorcardiographic loop[199-201] The inital 25 to 40 msec of the loop reflect the inferior infarction

The generated QRS forces are superior to the E point and rotate to the left along the X axis with the 25 and usually the 30 msec vector superior to the X axis[11, 201] The loop then turns superiorly and changes its rotation from clockwise to counterclockwise so that the bulk of the QRS loop lies superior to the X axis[199-201] Thus while the initial forces reflect the inferior infarction the terminal forces reflect the superior divisional block A frequent electrocardiographic problem is the interpretation of records displaying QS or QRS complexes in leads 2 3 and aV$_F$ When a frontal loop as just described is present combined inferior infarction and superior divisional block is evident[200] However if the frontal loop is markedly superior but exhibits clockwise rotation throughout the diagnosis is inferior infarction probably extensive but without combined superior divisional block[199] As Benchimol has pointed out the combined diagnosis is of great predictive value in assessing possible coronary artery obstruction since inferior infarctions are generally associated with right coronary artery lesions, while the superior division of the left bundle is nourished by the left anterior descending artery[200] Thus when the combined diagnosis is made double coronary vessel disease should be suspected clinically

In other patients with inferior infarction the axis is markedly vertical or even rightwards despite the initial prolongation of superior forces characteristic of inferior infarction[201-203] Here the diagnosis is inferior infarction combined with inferior divisional block This is a combination probably described previously by First and associates[204] as inferior infarction with "peri infarction block In some patients with inferior myocardial infarction injection of contrast material into the right and left coronary arteries successively produces an associated inferior and

opposite picture in the frontal plane.[13, 1] The initial forces are oriented superiorly and usually to the left, and the major QRS vectors are always directed inferiorly and usually to the right.[1, 3, 194] The loop rotation in the frontal plane is practically always clockwise. The late rightward forces observed in the frontal plane, of course, are also apparent in the horizontal plane, which maintains its normal counterclockwise rotation with initial forces inscribed anterior and to the left. It is apparent from this description that the QRS loops in the horizontal and frontal plane of inferior divisional block closely resemble the description of loops in Type C right ventricular hypertrophy as commonly observed in mitral stenosis, emphysema, and cor pulmonale.

Superiorly displaced frontal loops resembling those of superior divisional block may also occur with emphysema. Hyperkalemia may occasionally present with a marked superior or inferior frontal axis which may indeed represent superior or inferior divisional block, respectively, as these changes are reversible with correction of the electrolyte abnormality.[1, 7] A special type of counterclockwise superior frontal loop is commonly seen in patients with endocardial cushion defects.[1, 5] In these cases, the anatomic length of the superior division is prolonged as it courses along the anterior surface of the defect, while the inferior division is much shorter. This discrepancy in length results in sequential rather than simultaneous activation of the myocardium supplied by the superior and inferior divisions, respectively, with a resultant superior counterclockwise frontal loop resembling in every way superior divisional block.

Right bundle branch block combined with superior divisional block (references 2 to 16, 189 to 196)

When right bundle branch block is combined with superior divisional block, the terminal conduction delay oriented to the right and anterior with clustered time dashes is unchanged.[1, 9] However, a marked superior shift in the frontal plane axis occurs with the body of the QRS loop prior to the terminal appendage being inscribed well above the X axis and with counterclockwise rotation—as in the case of uncomplicated superior divisional block. The initial QRS forces are practically always inferior in location and may be inscribed either to the right or to the left.[90]

In the transverse or horizontal plane, two morphologies designated types A and B by Lichstein and associates[1] have been described and confirmed by several other observers.

In the more common type A horizontal loop, the body of the loop is inscribed counterclockwise and to the left with the maximum vector either anterior or posterior. The terminal appendage then follows characteristically oriented to the right and anterior of the E point. In the type B horizontal loop, the sense of rotation is clockwise with the entire QRS loop oriented to the E point.

In several clinical investigations attempts have been made to correlate these type B loops with associated dorsal myocardial infarction or right ventricular hypertrophy, but without significant success, as the majority of such cases lack other stigmata of these conditions. However, the type B loops are associated with a somewhat higher incidence of proven organic heart disease, ventricular hypertrophy, etc.[1]

In the author's view, the type B loops probably represent additional delay in the anterior or midseptal fascicle of the left bundle branch system. Delay in that branch would account for anterior displacement of the QRS loop and for the clockwise rotation observed without invoking additional hypertrophy or infarction. In this type B loop of right bundle branch block combined with superior divisional block, the vectorcardiographer encounters yet another circumstance in which overdiagnosis of prominent anterior forces, in this instance combined with clockwise rotation, may easily lead to mistaken diagnoses of serious organic heart diseases. At least partial confirmation of the concept of anterior conduction delay in the genesis of the type B loop is found in the work of Cohn and colleagues,[8] who demonstrated a variety of ventricular aberrations following stimulated atrial premature beats, some of which exhibited vectorcardiographic loops identical to the type B loop described above in the absence of dorsal infarction or right ventricular hypertrophy and which were intermittent. At slower heart rates the vectorcardiographic loops in these individuals were perfectly normal.

Right bundle branch block combined with inferior divisional block (references 197, 198)

The combination of complete right bundle branch block with inferior divisional block is considerably less frequent than the combination of right bundle branch block with superior divi-

sional block[197, 198] However the frontal plane vectorcardiographic loop is quite characteristic and easy to recognize The initial forces are always superior and may be oriented to the left or right The major axis of the loop is distinctly vertical close to the Y axis and terminal slowing oriented to the right is always present as in uncomplicated right bundle branch block

Various configurations of the QRS loop have been described in the horizontal plane with clock wise counterclockwise and figure of eight loops occurring with about equal frequency In the series of Varriale and Kennedy[198] who reported 12 patients with this combination all the horizontal plane loops initial forces were anterior or directly leftwards *The horizontal plane loops present* terminal rightward anterior conduction delay with clustering of time dashes characteristic of right bundle branch block Many horizontal loops of patients with combined right bundle branch block and inferior divisional block have very prominent anterior QRS forces unrelated to the presence of dorsal myocardial infarction or of right ventricular hypertrophy Thus this particu lar combination of divisional blocks again pre sents the opportunity for overdiagnosis of promi nent anterior QRS forces Five of Kennedy and Varriale s patients had well established inferior infarction in addition to their conduction disor ders and in two anterior infarction was also present Before the diagnosis of right bundle branch block combined with inferior divisional block is made four other entities must be consid ered These are right bundle branch block com bined with one of the following right ventricular hypertrophy chronic pulmonary disease slender body build or extensive lateral infarction

Ordinary clinical examination is usually suffi cient to rule out the first three of these possibili ties and in the last abnormally large and pro longed early rightward forces might suggest the correct diagnosis

Obviously right bundle branch block combined with inferior divisional block produces a marked vertical shift in the frontal plane axis while right bundle branch block combined with superior divi sional block produces a marked superior shift in the frontal plane axis In some patients with chronic right bundle branch block the associated inferior or superior divisional block may be inter mittent and i was from observations of axis shift in such cases that Rosenbaum [7] first deduced logically the concept of a multidivisional con ducting system arising from the left bundle branch

Myocardial infarction combined with superior or inferior divisional block (references 2 to 16 199 to 209)

Inferior myocardial infarction combined with superior divisional block results in a characteris- tic and easy to recognize frontal vectorcardio- graphic loop[2] [1] The inital 25 to 40 msec of the loop reflect the inferior infarction

The generated QRS forces are superior to the E point and rotate to the left along the X axis with the 25 and usually the 30 msec vector superior to the X axis[11] [1] The loop then turns superiorly and changes its rotation from clockwise to coun terclockwise so that the bulk of the QRS loop lies superior to the X axis[199] [01] Thus while the initial forces reflect the inferior infarction the terminal forces reflect the superior divisional block A frequent electrocardiographic problem is the interpretation of records displaying QS or QRS complexes in leads 2 3 and aV_F When a frontal loop as just described is present combined infe- rior infarction and superior divisional block is evident [9] However if the frontal loop is marked ly superior but exhibits clockwise rotation throughout the diagnosis is inferior infarction probably extensive but without combined superior divisional block[199] As Benchimol has pointed out the combined diagnosis is of great predictive value in assessing possible coronary artery obstruction since inferior infarctions are generally associated with right coronary artery lesions while the superior division of the left bundle is nourished by the left anterior descend ing artery [00] Thus when the combined diagnosis is made double coronary vessel disease should be suspected clinically

In other patients with inferior infarction the axis is markedly vertical or even rightwards despite the initial prolongation of superior forces characteristic of inferior infarction[203-205] Here the diagnosis is inferior infarction combined with inferior divisional block This is a combination probably described previously by First and asso- ciates [6] as inferior infarction with peri infarc tion block In some patients with inferior myo- cardial infarction[17] [1] [9] injection of contrast material into the right and left coronary arteries successively produces an associated inferior and

then superior divisional block on a temporary basis The combination of inferior infarction with inferior divisional block produced by such experiments is quite similar to loops described as inferior infarction with peri infarction block

In contrast to the above anterolateral infarction accompanied by superior divisional block would result in a frontal plane loop characterized by abnormally prolonged and large initial rightward forces (lateral infarction) followed by a continuation of the loop superiorly and counterclockwise in the left superior quadrant of the frontal plane—with these terminal forces characteristic of superior divisional block Thus the criteria for so called peri infarction block would be met with the initial vectors opposite the terminal vectors Experimentally patients with anterolateral infarction may have a picture closely resembling peri infarction block superimposed by selective injection of the left coronary artery

Although the author believes that most cases described as peri infarction block probably represent infarction combined with a divisional block it still remains possible that in some instances the conduction disturbance is indeed peripheral and is localized in the ischemic tissue around the necrotic zone of the infarction [08]

Since the diagnoses of superior or inferior divisional block are made from the frontal plane vectorcardiogram which does not display anterior/posterior forces the diagnosis of associated anterior infarction rests with the disposition of the initial vectors in the horizontal reference plane

Thus characteristic deformities as described in the section on anterior infarction will co exist with typical terminal frontal loop abnormalities characteristic of either superior or inferior divisional block as described above One special variety of infarction combined with divisional block deserves particular mention This is true dorsal infarction combined with inferior divisional block Here in the transverse plane the initial half of the loop is displaced anteriorly to the left anterior quadrant of the horizontal plane while the major axis in the frontal plane is oriented inferiorly with clockwise rotation This vectorcardiographic QRS loop obviously closely resembles Type B or Type C right ventricular hypertrophy but in fact may on occasion really represent a combination of inferior divisional block with anterior conduction delay The reader is reminded that anatomical studies reveal that the anterior fascicle of the left bundle branch frequently arises from the inferior division Thus fibrosis or scarring of that division proximal to the bifurcation into the inferior and midseptal divisions could well account for this last vectorcardiographic picture described

The entire subject of myocardial infarction complicated by intraventricular conduction disturbances is beautifully outlined in program form by Lemberg and Castellanos in their book Vectorcardiography

In that text and in at least one publication [09] Castellanos advances the concept of intra infarction block. This diagnosis is to be suspected when the Q waves produced by an infarction or the corresponding portion of the vectorcardiographic loop exhibit slurring or notching lasting 20 msec. The genesis of this abnormality may well be islands of living myocardium within the infarcted zone These islands by contributing relatively normal QRS voltages during the subtraction effect of the infarcted tissue surrounding result in an interruption of the usually smooth initial defect resulting from the infarction [09] This is an interesting and valuable conception and may well explain the observed phenomenon which is encountered occasionally in vectorcardiographic tracings.

Right bundle branch block combined with myocardial infarction (references 2 to 16 199 to 209)

When right bundle branch block is combined with inferior wall infarction the diagnosis is quite easy by vectorcardiogram The reason is simple enough The right bundle branch block, which displaces the terminal QRS forces right and anteriorly as previously described is not only a distal phenomenon in the QRS loop but is most evident in the horizontal reference plane Although the terminal rightward delay is evident in the frontal plane the initial 25 to 40 msec of the QRS loop are not affected and still will reveal the characteristic abnormality of myocardial infarction of the inferior wall

Lateral myocardial infarction which is generally diagnosed on the basis of a prolongation of initial rightward forces beyond the normal value of approximately 25 msec is likewise evident in both the horizontal and frontal references even

cardiogram exhibiting left bundle branch block, accurate localization is possible in about half the cases although many remaining patients do indeed have infarctions but in unexpected areas Goldman and Pipberger[11] have identified other criteria useful in recognizing infarction in the presence of left bundle branch block An absence of an anterior ST junctional displacement was indicative of infarction at the 95th percentile level and a T magnitude in the horizontal plane of less than 0 2 millivolts was also indicative of infarction at the 95th percentile level Goldman and Pipberger[11] also confirmed the importance of initial rightward QRS forces or prominent anteri or forces as criteria for myocardial infarction in the presence of left bundle branch block In the series of Goldman and Pipberger the total iden tification rate was 50% with 14% false positives These results were approximately equal to the diagnostic power of the vectorcardiogram in iden tifying myocardial infarction in the presence of right bundle branch block These autopsy con firmed VCG patterns for myocardial infarction in the presence of left bundle branch block resemble very closely the vectorcardiograms produced by Bisteni and colleagues [212] who used phenol injec tions to induce areas of necrosis in experimental animals with previously induced left bundle branch block The above data are rather convinc ing in establishing the value of vectorcardiogra phy in the assessment of patients presenting with left bundle branch block and in whom coronary artery disease with infarction or myocardial fibrosis is suspected clinically

Incomplete left bundle branch block

In so called incomplete left bundle branch block the total duration of the QRS loops is between 100 and 120 msec In general these loops resemble those of left bundle branch block except that the duration is shorter In the characteristic case the initial forced are oriented to the left and anterior in the horizontal plane which may retain its u ual counterclockwise rotation but occasion ally is figure of eight with the proximal section coun erclockwise and the distal section clockwise

The frontal loop is oriented close to the X axis but not above it with characteristic counter clockwise rotation Scalar electrocardiographic features of left ventricular hypertrophy are often present in these cases

Right ventricular hypertrophy with left bundle branch block (reference 223)

A little known application of the vectorcardio gram in left bundle branch block is the diagnosis of right ventricular hypertrophy Chou and Helm[223] described five patients with unequivocal right ventricular hypertrophy whose vectorcar diograms could easily be recognized as typical o left bundle branch block The contour of th horizontal loops the mid and terminal slowing and the clockwise rotation were all characteristic The QRS loops were prolonged and the initia QRS forces were oriented to the left and inferior ly However in two ways these loops differe from the typical uncomplicated stereotype of lef bundle branch block These were the rightwar displacement of the body of the QRS loop and th leftward orientation of the ST vector and T loop

Although as described above rightward dis placement of QRS may be seen in left bundl branch block complicated by myocardial infarc tion there are distinct differences from Chou and Helm s patients[2 3] with right ventricular hyper trophy When marked rightward deviation i present secondary to infarction in left bundl branch block the displacement is initial or termi nal with the bulk of the loop still oriented to th left and posteriorly Further when early force are displaced to the right in myocardial infarctio complicated by left bundle branch block th rotation is generally rightward and clockwis *about the E point* whereas in left bundle branch block complicated by right ventricular hypertro phy the early rotation about the E point i counterclockwise The cardiologist is encourage to become familiar with the normal stereotype o left bundle branch block and with the variation described from which myocardial infarct on o right ventricular hypertrophy may be suspected In the author s opinion patients with left bundl branch block present frequent opportunities fo additional diagnosis from the vectorcardiogram and the test should be employed frequently i these individuals

Right bundle branch block combined with righ ventricular hypertrophy (references 2 to 16 224 to 228)

Baydar and colleagues presented a classifica tion of right bundle branch block in relation t right ventricular hypertrophy and chronic pulmo

diagnosis beyond the conduction disorder is ble However a surprising amount of infor is available from careful examination of loops in left bundle branch [1] Indeed Goldman and Pipberger have emonstrated that vectorcardiographic criteria e about as accurate in identifying the presence of myocardial infarction accompanying left bun e branch block as in the case of right bundle branch block

In order to use the vectorcardiogram properly in left bundle branch block the cardiologist must become familiar with the stereotype of left bundle branch block as it is encountered in the absence of cardiac abnormality or as produced mentally [1] Under such circumstances a rather typical picture is seen The initial QRS forces are oriented to the left and anteriorly and always rotate in a counterclockwise manner with a duration of anterior forces about 10 to 20 msec [1] The second vectorial movement as out lined by Scott [11] is directed leftward posteriorly and inferiorly attributed by Bisteni and col leagues [1] and also by Wallace and associates to right to left activation of the interventricular septum At about 50 msec the third vector appears This is directed leftward superior and posterior and exhibits slurring and clustering of time dashes Here the rotation changes from counterclockwise to clockwise and this sense of rotation persists for the duration of the QRS loop as seen in the horizontal plane The last vector the fourth which corresponds to the returning limb or the afferent portion of the QRS loop is oriented posterior and left and is attributed to activation of the left ventricular free wall The closest spacing of time dashes is during the inscription of the third vector described above

In the frontal reference plane the initial forces are oriented to the left and inferiorly The loop is inscribed in a counterclockwise manner usually inferior to the X axis although the terminal forces may be inscribed above the X axis The T loop in the horizontal plane is oriented to the right and anterior and is usually counterclockwise while in the frontal plane it is right and inferior and also counterclockwise [m] Neuman and colleagues and Pietras and co workers have evaluated various criteria for myocardial infarction in patients with left bundle branch block followed to necropsy and subjected to detailed postmortem examination of the heart In all six variations from the typical stereotype of left bundle branch block were considered and evaluated as infarction criteria Clockwise rotation of the initial forces of the QRS loop about the E point in the horizontal plane was evaluated as a criterion for septal infarction Of 13 such patients all had myocardial infarction or fibrotic areas six of which were concentrated in the ventricular septum The remaining patients had infarction or fibrosis in other myocardial areas A posterior position of the 01 sec vector as seen in the horizontal plane was tested as a criterion for anterior apical infarc tion Of nine such patients four had infarction or fibrosis of the anterior wall and the remaining five had fibrosis or infarction but located in other areas

Rightward displacement of the afferent limb (but not crossing to the right of the E point) was evaluated as a criterion for lateral infarction Six patients presented such vectorcardiograms and five had either infarction or fibrosis of the lateral wall The remaining patient had a septal infarct

Displacement of the afferent limb of the QRS to a point greater than 0 05 millivolts to the right of the E point was evaluated as a criterion of anterolateral infarction Of 14 patients with this abnormality seven had infarction or fibrosis in the anterior and lateral areas six patients had infarction or fibrosis in other areas and one patient had left ventricular hypertrophy An anterior position of the 02 5 sec vector was evaluated as a criterion for true posterior infarc tion Seven patients met this criterion of whom five indeed had posterior infarctions at necropsy The remaining patients had infarction or fibrosis in other areas A superior frontal mean axis (between −30 and −180 degrees) was evaluated as a criterion for myocardial infarction Of 21 patients with such a superior axis 14 had infarc tions demonstrated at autopsy In the largest group (ten patients) the infarction was dorsal in location All the remaining patients had infarc tion or fibrosis in other areas and several had ventricular hypertrophy as well In comparing the performance of vectorcardiographic versus electrocardiographic diagnosis it was very evi dent that the vectorcardiogram was quite superior in the diagnosis of infarction in the present of left bundle branch block [-1] However the authors of these studies point out that when criteria for infarction are met by a vector

ular system an initial delay is noted in the QRS loop which is directed away from the point of origin of the ectopic beat In this respect, such loops are similar to those generated by pacemaker stimuli or via AV bypass tracts in the pre excitation syndromes [31]

After the initial delay, which varies in duration from 20 to 40 msec rapid conduction may follow usually oriented in the same direction as the initial forces This probably represents entrance of the activation wave into an adjacent fascicle A change in direction then commonly occurs as myocardium not activated by the initial fascicle depolarizes and this in turn is followed by slow activation of the ventricle opposite the site of initial ectopy When the ventricular point of origin of the premature beat is not near a segment of the fascicular system the initial delay may not be followed by as many directional changes until activation of the opposite ventricle occurs [9]

Probably the most importance feature of vectorcardiography in ectopic ventricular beats is the detection of the initial slowing which serves to locate the point of origin of the ectopic beat [31] As has been pointed out by several authors inspection of the scalar ECG or even of orthogonal leads may not be sufficient in localizing this initial delay which may be apparent only as a step in the VCG loop [2 9 3 23]

Talbot and associates have located the initial forces in vectricular ectopic vectorcardiograms using the 360 degree planar reference system for the frontal and horizontal planes It is evident from their data that these initial slow forces may be located anywhere indicating a large variety of possible ventricular sites of origin in either ventricle The majority of initial delays were located to the left of the E point in the frontal plane mostly inferior and either anterior or posterior to the E point when considered in the horizontal plane The rotational characteristics of the QRS loops resulting from ventricular ectopy were highly variable Clockwise rotation in the horizontal plane was a common finding

The QRS loops resulting from pacemaker stimulation are similar in many ways to the vectorcardiographic loops arising from spontaneous ventricular ectopy The entire QRS loop is prolonged in duration owing to conduction delay in the ventricle opposite the one stimulated Thus with right *ventricular stimulation the major axis of* the induced QRS loop is leftward and the opposite situation prevails with left ventricular stimulation [219 2 0] Pacemaker stimulation inferior in a ventricle will result in a superiorly directed QRS loop while electrodes placed in the outflow tract will result in inferiorly placed loops Similar considerations apply to anterior and posterior direction—with anterior positioning resulting in posterior loops Castellanos and co workers have succeeded in reproducing spontaneously occuring VPC configuration by selective stimulation of various portions of the right ventricle or left ventricle by placement of the pacing electrode at the right ventricular apex in the coronary sinus or within the middle cardiac vein

An invariable feature of pacemaker vectorcardiographic loops is an initial delay entirely similar to that seen frequently in ventricular ectopy This initial delay is most frequently oriented inferior and left about half are anterior and half are posterior [39] The body of the QRS loop may be clockwise counterclockwise or figure of eight in all three reference planes with the commonest finding a figure of eight loop in both horizontal and frontal planes [31 33 241] Since infarction induces changes in the vectorcardiographic loops of left bundle branch block (which right ventricular paced loops resemble) attention has been paid to similar changes in the pacemaker VCG loops of patients with underlying myocardial infarction [3 237 41] Not surprisingly the induced QRS loops are indeed modified and resemble very closely the variations produced in spontaneous left bundle branch block by myocardial infarction as occuring under natural or experimentally induced conditions [1] With inferior myocardial infarction the right ventricular paced vectorcardiographic loop is oriented superiorly with initial delay also oriented superiorly and with clockwise rotation of the frontal plane loop [235 241] In true posterior infarction the initial delay was oriented markedly left and anterior with counterclockwise rotation of the induced horizontal loop This picture according to Zoneraich and Zoneraich [23] *is unique* With infarction of the anteroseptal areas the initial QRS vectors were oriented right and posterior with clockwise rotation of the horizontal plane loop—thus closely resembling the alterations produced in naturally occuring left bundle branch block complicated by anteroseptal infarction [19 0] The stimulus artifacts from unipolar catheters are about ten times larger than those produced with *bipolar*

ary disease based upon the horizontal plane on of the afferent (returning) limb of the QRS loop Thus in patients with an afferent limb r to the E point no right ventricular hypertrophy or pulmonary disease was expected In a second group the afferent limb was anterior the E point but the loop rotation remained clockwise Here an increased incidence of ventricular hypertrophy and chronic pulmonary disease was encountered In the third group only was the afferent limb anterior to the E point but the entire loop exhibited a clockwise Here the incidence of right ventricular y or chronic pulmonary disease was the highest

In a recent re evaluation of these criteria Fedor and colleagues[226] confirmed an increasing idence of cardiac failure or severe pulmonary as vectorcardiograms were arranged ig to these three groups designated as Types I II and III Although Fedor and associates concluded that the Type III variety was a reliable guide to cardiac failure or severe pulmonary disease—and indeed even to pulmonary hypertension their data indicate that five of 31 patients falling into this Type III group (16%) had only insignificant cardiac or pulmonary disease The reader is here referred to prior discussion of right bundle branch blocks combined with divisional block induced by atrial premature stimulation This commonly results in transient aberration and vectorcardiographic loops identical with the Type III variety as commonly encountered clinically and associated with chronic pulmonary disease

Chou and associates studied children with right ventricular hypertrophy determined at cardiac catheterization who had both pre and post operative vectorcardiograms with the latter exhibiting a new right bundle branch block These patients without question reflected in their second vectorcardiogram the combination of right bundle branch block associated with right ventricular hypertrophy Chou and colleagues were unable to confirm that clockwise rotation in the horizontal plane was a reliable indicator for such right ventricular hypertrophy as the sense of rotation changed in 50% of the operative patients who developed postoperative right bundle branch block However these authors did offer three criteria which were useful in children[22] These were a maximum QRS vector directed to the right of 65 degrees in either the horizontal or frontal plane a maximum rightward vector exceeding the normal value for age (generally a value greater than 1 0 millivolts) and lastly an abnormal ratio of leftward to rightward QRS forces (RX/SX) the critical value being 0 91 in the oldest age group studied (ages 10 to 16 years)

The T loops in right ventricular hypertrophy with or without bundle branch block are oriented to the left with clockwise rotation in the horizontal plane and are usually located posterior to the E point[26] Additional discussion of the T loops in right bundle branch block and in RVH is to be found in a subsequent section devoted entirely to T loops Clearly the vectorcardiographer attempting the diagnosis of RVH in the presence of a right bundle branch block on the basis of a prominently anterior and clockwise horizontal loop is liable to make mistakes A very similar picture as described above has been found with right bundle branch block combined with superior divisional block or combined with true dorsal infarction Conduction delay in the anterior fascicle may also play a role especially when another divisional block is already present However when even a modicum of clinical information is available the vectorcardiographic diagnosis may be pronounced with more authority

The vectorcardiography of premature ventricular or pacemaker induced complexes (references 229 to 242)

Despite the technical difficulty in obtaining vectorcardiograms of ventricular premature contractions several authors have accumulated a sizable series of such beats [30 1 33] Although several varieties of loop disturbances have been described they are readily understandble in the light of published information on the vectorcardiography of bundle branch and fascicular blocks

For example about twenty % of ventricular premature beats exhibit vectorcardiograms which are indistinguishable from uncomplicated right or left bundle branch block.[2 9] It may be presumed that the beats resembling right bundle branch block arise in the left main bundle branch while those resembling left bundle branch block arise in the right main bundle [1 2] The large majority of ventricular ectopic beats however are considerably more complex but nevertheless understandable When the ectopic focus is outside the fascic

direction or rotation abnormal width in addition is of little value in diagnosis as all presently described T loop abnormalities be they secondary to conduction delays hypertrophy or ischemia have the capacity to widen the T loop

Scalar electrocardiographers have long been used to the term primary or secondary T wave abnormalities and a parallel exists in vectorcardiography The secondary T loop abnormalities may be attributed to alterations in the repolarization sequence as seen in right or left ventricular hypertrophy and right or left ventricular conduction disorders[219, 231, 2, 6, 59, 61] Primary repolarization abnormalities are attributed to local disorders of recovery, usually in segmental ischemic zones of the left or right ventricles

The basic change in recovery physiology in an ischemic zone is a prolongation of action potential Thus the last portion of the myocardium to generate recovery potentials is the ischemic zone and owing to the return of the unaffected myocardium to resting potential by that time the observed T wave and T loop must be directed away from the area of ischemia Smith and colleagues[17] noted marked shifts in the direction of the T loops during right or left coronary artery injection respectively with contrast material Right coronary artery injection producing transient ischemia of the inferior wall resulted in a leftward and superior shift of the T loop resembling the direction observed in clinical inferior infarction with a surrounding ischemic zone In contrast left coronary injections caused a shift of the T loop to the right and inferior entirely similar to changes observed with lateral myocardial ischemia These changes were of course transient and reversible

Several authors have described the T loop abnormalities seen in coronary artery and other myocardial diseases [5, 6] In general ischemic T loops change in direction as noted above with their long axis directed away from the ischemic zone In addition the length/width ratio ch nges so that the loops are characteristicly ov ic with the most terminal portions of the T loo pposite the area of slow repolarization T a rather circular loop in which the early ba t forces may be anterior with the terminal posterior is commonly seen with anterio dial ischemia This type of loop results lus minus T wave in the precordial lead imilar considerations apply to inferior, lateral and dorsal ischemia. In this latter condition since the T loop is normally anterior and left the development of dorsal ischemia may shift the T to a directly anterior position However because of lateral ischemia which is often associated the most terminal T forces are oriented the most medially resulting in a change in rotation of the horizontal T loop from counterclockwise to clockwise In a T loop of normal width clockwise rotation in the left anterior quadrant is almost never seen in normals[2, 252] In the presence of clinically suspected coronary disease such a vectorcardiographic observation should be taken as evidence favoring dorso lateral ischemia Vectorcardiographic T loops exhibit another interesting characteristic in many cases The terminal T forces may exhibit slowing so that the entire loop is evenly inscribed, corresponding to the symmetrical T wave commonly encountered in scalar electrocardiography and recognized as characteristic of myocardial ischemia[2, 3, 5]

An excellent programmed introduction to the vectorcardiography of T loops was presented by Castellanos and colleagues It should be emphasized at this point that the vectorcardiographer interpreting an ischemic T loop is really considering three repolarization phenomena all simultaneous with the observed T loop the resultant In a case with a localized area of left ventricular ischemia the balance of the left ventricle may well be generating perfectly normal T potentials and a normal T loop The right ventricle may similarly be generating a normal right ventricular T loop Thus the observed T loop represents the summation of the normal left and right ventricular repolarization with the ischemic repolarization added

The secondary T loop abnormalities observed in left ventricular hypertrophy and the left ventricular conduction delays (left bundle branch block right ventricular pacing and ventricular premature beats arising in the right ventricle) are all very similar Since these conditions in the pure form do not affect the right ventricle the T loop generated by the right ventricle is in its usual position—anterior However the hypertrophy or conduction disorder affecting the left ventricle alters the recovery sequence so that the resulting T loop is directed opposite the observed QRS and becomes located to the right and anterior of the E point The right anterior T loop

timulation owing to the much greater distance etween the negative electrode and the pulse nerator in the case of a unipolar pacemakers compared to the approximately ten mm distance tween negative and positive poles with bipolar atheters [3] Therefore the stimulus artifact with unipolar pacemakers is directed from the catheter n to the anatomic location of the battery pack ver it has been implanted On the other hand with transvenous bipolar catheters placed the apex of the right ventricle the vector presenting the stimulus artifact is usually to the right and superior Much greater ariation is possible in the case of left ventricular ters which may be placed anywhere on the ventricular surface A change in axis of the stimulus artifact from a bipolar pacing catheter may result from wire breakage as the stimulation changes from bipolar to unipolar with the artifact axis now depending upon the location of the battery pack and the site of ventricular contact proximal to the break

Pacemaker vectorcardiography and the vectorcardiography of ectopic ventricular beats have provided a fascinating confirmation of the information so laboriously accumulated concerning bundle branch blocks fascicular blocks the preexcitation syndrome and their combinations with myocardial infarction

Zoneraich and colleagues [2] have correlated the electrocardiographic and vectorcardiographic findings resulting from right ventricular pacing with echocardiography of the intraventricular septum A posterior twitch of the left side of the *septum entirely similar to that described in* spontaneous left bundle branch block has been observed with pacemaker stimulation—except that this twitch occurs about 30 msec later (probably owing to the initial delay occuring with pacemaker excitation of the heart) No doubt future studies will extend these observations in which echocardiography and vectorcardiography are correlated

Vectorcardiography of the T loops (references 2 to 16 106 243 to 269)

Just as the QRS loops at any moment in time represent the sum of all electrical activity of the entire heart (right and left ventricles) so does the T loop represent the summation of recovery potentials in both ventricles simultaneously [2] That the right ventricle contributes to the T loop should be no surprise to any cardiologist familiar with the obvious T abnormalities seen in conditions such as right bundle branch block and right ventricular hypertrophy Obviously the right ventricle is capable of generating very large recovery potentials which may indeed dominate the observed T loop

Similarly in the normal the observed T loop is the resultant of a leftwards T loop generated by the left ventricle added to a directly anterior T loop generated by the right ventricle [2 3 6 17] It is the sum of these two separate repolarization phenomena that results in the normally observed T loop directed to the left inferiorly and anteriorly—thus making a rather wide angle in the horizontal plane with the left and posterior QRS loop

The electrophysiology of repolarization has been presented by several authors [4] as has the morphology of the normal vectorcardiographic T loop [2 5] In addition to the directional characteristics mentioned above the normal T loop rotates in a counterclockwise manner in the horizontal plane and is either narrow or clockwise in the frontal plane Some normal T loops are so elongated and slender that rotational description has little meaning Indeed some authors recommend that no description of rotation be made when the length with ratio of a T loop in any plane exceeds 10 to 1 Ordinarily the early portions of the T loop are written more slowly than the terminal portion accounting for the asymmetric T wave seen in surface scalar recordings [2 2 5] Thus several characteristics *of the normal may be altered by changed physiol*ogy or disease states—that is the direction sense of rotation the length/width ratio and the speed of inscription

Chou and associates have emphasized the spatial length/width ratio in the normal and determined an upper limit of 1 6 This is calculated by dividing the maximum length in any plane by the maximum width in any plane Occasionally the only abnormality found in a vectorcardiographic record may be an alteration in the length/width ratio such that the loop becomes ovoid with a ratio less than 1 6 In the absence of drugs such as digitalis which may cause a similar alteration such a reduction in the length/width ratio should call attention to the possibility of organic heart disease When other T loop abnormalities are present such as abnormal

the T loop persists but the sense of rotation changes from counterclockwise to clockwise in the horizontal plane and the T loop shifts to a posterior leftward position again with an open QRS loop Isaacs and colleagues [3, 4] recommend simultaneous recording of the Frank XYX leads as a useful monitoring technique in exercise stress testing Although they recorded the vectorcardiographic loops simultaneously with exercise the use of magnetic tape recordings would permit a later generation of loops and the use of signal averaging as well [10] Rautaharju and co workers [1] have subjected P ST and T voltages obtained using the Frank lead system during exercise to computer analysis Bizarro and associates recently reported the correlations of various vectorcardiographic criteria with myocardial scarring determined at autopsy Surprisingly the most sensitive criteria found related to T wave voltage in the X Y and Z axes It seems possible therefore that the entire question of specificity of vectorcardiographic T loop criteria should be re explored

Vectorcardiography of the P loop (references 2 to 16 269 to 289)

The technical problems that complicate P loop study arise from the small amplitude of the voltages generated by atrial depolarization necessitating extremely high gain for proper analysis Standardization of one millivolt equal to 20 or 40 cm have been commonly used and even higher sensitivities are possible Several different techniques have been used in order to eliminate overlying portions of the T or QRS loops These techniques include gating in which only the desired portion of the cardiac cycle in this case the P wave is recorded recording on tape followed by averaging by computer and then followed by gating or the technique of examining running or timed loops in which the oscilloscopic beam moves from left to right while the loops are being inscribed Using these technologies as well as simple high quality still loop vectorcardiography a good deal of information has been accumulated about the vectorcardiography of the P complex

Two distinct components of the P loops may be observed which in the normal person are distinctly different in magnitude and direction The initial right atrial component is directed to the left and anterior[l] [...]le the left atrial component occurs later [...] directed left and posteri-orly [2, 2, 4, 6] When the Frank electrode system is used the maximum P vector in the frontal plane is oriented between +30 and +90 degrees (inferior and left) while the maximum vector in the horizontal plane is oriented between −4[...] a[nd] −20 degrees (left and posterior) The magnitude of the maximum horizontal vector of the P loop [is] less than 0 12 millivolts Criteria have been proposed by several workers for the identification of right or left atrial overload The term overload seems preferable at this time to either hypertrophy or dilatation as changes in intra atrial pressure or size may result in identical P loop abnormalities as observed in true hypertrophy (increased atrial wall thickness) [2, 3] Indeed the term overload may itself be too restrictive a[s] intra atrial conduction disorders which will al[so] be discussed may produce P loops closely resembling those observed in left atrial overload In right atrial overload the horizontal P loop shifts to a distinctly left anterior position and to a more vertical position in the frontal reference plane [1, 2, 3] However the duration of the P loop does not increase and therefore remains less than 100 msec in all reference planes The maximum vector in the horizontal plane may be found between +6 and +90 degrees (the left anterior quadrant of the horizontal plane) and in the frontal plane between +50 and +120 degrees (inferior and often rightwards) The magnitude of the maximum anterior deflection exceeds 0 1 millivolts and the ratio of posterior to anterior P loop forces is usually less than one averaging 0 [...] in the experience of Benchimol and associates [6] The P loop rotation in right atrial overload is characteristically counterclockwise in both the frontal and horizontal reference planes The magnitude of the major P vector in the frontal plane is increased and equals or exceeds 0 2 millivolts

Left atrial overload In general although the magnitude of the major anterior P vector remains unchanged from normal (mean value 0 04 millivolts) the magnitude of the posterior P vector distinctly increases exceeding the normal mean value of 0 12 millivolts [7] Further the ratio of posterior to anterior P voltage increases and exceeds 2 The maximum horizontal vector is located between −10 and −90 degrees (left and posterior) while the maximum P frontal vector is located between +60 and −10 degrees (distinctly less inferior than patients with right atrial overload) A figure of eight rotation is common in the

. i secondary to the left ventricular disorders is characteristicly counterclockwise in ... horizontal reference plane[106] Controversy ... exists about the diagnostic significance of a ...se horizontal T loop located in the right anterior quadrant of the horizontal plane in the presence of left ventricular hypertrophy or a left ...ntricular conduction delay[106] Although originally believed to represent coronary artery dis... in addition to the secondary T loop abnor... sufficient evidence has been presented ... arteriography of such patients to indi... that uncomplicated left ventricular hyper... especially with a rather rightward hori... T loop may result in a clockwise rotation of the T in the absence of significant coronary obstruction[2,9] However in the presence of left bundle branch block such rotation probably does ...icate that in addition to the secondary T loop ...ty attributable to the conduction disor... an additional ischemic zone exists[96] In that ...circ...ce three simultaneous T phenomena would again be responsible—that is the normal right ventricular T the secondary left ventricular T and an ischemic left ventricular T

Somewhat similar but occasionally more complicated considerations apply to secondary changes in the T loop generated by the right ventricle[59, 2] Here in the presence of severe right ventricular hypertrophy or right ventricular conduction delays (right bundle branch block left ventricular pacing or ectopic beats arising from the left ventricle) the sequence of recovery is altered in the right ventricle such that the observed T loop is located in the left posterior quadrant of the horizontal plane and typically with clockwise rotation As might be expected from this comment there is no observable difference between the T loop in right ventricular hypertrophy and the T loop in right bundle branch block

Rubler and associates[5] did note that in right bundle branch block complicating clinically established right ventricular hypertrophy the T loop tended to be more posterior than in uncomplicated right bundle branch block The rotation however remains clockwise most commonly and the length/width ratio is often abnormal in both conditions

Obviously if the vectorcardiographer confronts a QRS loop characteristic of right bundle branch block but with a T loop oriented to the right and anterior or posterior a left ventricular abnormality complicating the right bundle branch block must be considered Associated severe left ventricular hypertrophy could be responsible or an ischemic zone in the left ventricle

Uniformity of inscription of such a T loop as well as its location helps to identify ischemia as the cause of the unexpected location of the T loop[4]

The T loop abnormalities which accompany divisional block have not been well worked out In many cases the T loops remain entirely normal However in some examples observed personally or published in atlases with superior divisional block the T loop has all the characteristics of the secondary T loop abnormality observed with left ventricular hypertrophy or left bundle branch block

In some cases of anterior conduction delay the T loops are perfectly normal while in others they assume a posterior position

Just as myocardial ischemia in a single zone may alter the direction shape and rotation of a T loop already influenced by hypertrophy or conduction delay several coexisting ischemic zones may modify one another Thus inferior ischemia combined with lateral ischemia characteristically displaces the T loop right and superior The sense of rotation varies with the terminal T forces directed away from the most ischemic area

T loops should be recorded at moderate high amplification and with gating circuits when possible to remove overlapping segments of QRS and T A useful technique is to alter the interval between time dashes during the T loop recording so that 10 msec separates each dash rather than 2 or 2 5 msec This results in a more readily appreciated sense of rotation

T loop abnormalities after exercise have been reported[26, 6, 3] and correspond quite closely to the ST T abnormalities found in abnormal stress testing Isaacs and colleagues[3, 6] have correlated three different T loop patterns with the three characteristic ST responses to exercise ST junctional depression with an upsloping ST segment has been correlated with an elongated horizontal T loop which remains open at its termination When the ST segment is depressed and isoelectric a wide ovoid horseshoe shape T loop is seen again with an open QRS loop In the most severely abnormal response downsloping ST segment depression the horseshoe shape of

tion delay and the vectorial orientation of these initial forces is directed away from the point of origin of the ectopy, or from the insertion of the bypass tract in the case of W P W

Classifications of W P W by vectorcardiography have described two basic orientations of the initial conduction delay which has a duration varying from 20 to 70 msec Delays oriented anteriorly were designated as Type A and presumably originated from early activation of the posterobasal wall of the left ventricle Type B resulting from early activation of the right ventricular free wall produced delta vectors directed to the left[2 0 2]

In either of these varieties the initial delay could be oriented in a marked superior direction thus mimicking inferior wall infarction[2V1 2] In addition the Type B delta vector if oriented posteriorly would mimic anterior infarction and the Type A QRS loop oriented largely to the left and anterior of the E point could mimic dorsal infarction or right ventricular hypertrophy

More recently[6] the above classification has been expanded Castellanos and co workers[7 9] have recommended that the right ventricular entrances be subdivided into posterior and anterior types The anterior entrance type in Type B exhibits a delta vector directed to the left and posterior while in the posterior entrance type the delta vector is directed to the left and slightly anterior to the X axis In contrast the Type A delta vector is markedly anterior resulting in positive delta and QRS complexes in Leads V_1 and V_2 of the scalar electrocardiogram Tonkin and associates made the important observation that all septal bypass tracts produced a superior 10 msec vector in the frontal plane while all free wall bypass tracts resulted in inferiorly oriented 10 msec vectors Thus determination of the spatial orientation of the initial conduction delay in W P W serves not only to identify the left or right ventricle as the site of entrance but attention to the frontal plane axis may separate free wall from septal bypass tracts Such identification has important surgical implications

Following the initial delay of the delta vector activation of the ventricular masses occurs as a fusion complex between the activation wave generated from the bypass site entrance and the normal activation via the His Purkinje system[51 56] If the activation through the normal conducting system dominates the QRS loop after the delta vector may be largely normal

However if conduction through the bypass trac dominates the conduction through the AV nod and His Purkinje system is delayed varyin degrees of fusion complexes occur producing th electrocardiographic concertina effect described by Portillo[3 1] If activation occurs entire through the bypass tract conduction delay evident throughout the entire QRS loop whi becomes greatly prolonged In the case of Type pre excitation the terminal delay will be orient to the right but usually posterior and does n resemble the common variety of right bund branch block in which the terminal delay oriented to the right and anterior Similarly Type B with pure bypass tract activation of t ventricles conduction delay will be eviden throughout a loop oriented to the left and posterior and which will superficially resemble left bundle branch block[4 97]

An excellent programmed presentation of electrocardiography and vectorcardiography in the W P W syndrome with and without complicating bundle branch blocks was presented by Castellanos and co workers[7] An especially interesting problem is presented by the combination of pre excitation with bundle branch block[4] This is a distinctly different phenomenon from the vectorcardiogram produced by complexes representing total excitation via the bypass tract[2 901] In Type A W P W with early excitation of the left ventricle, a coexistent right bundle branch block is perfectly possible Several patients with early excitation of the left ventricle and coexistent right bundle branch block have been reported, and in others the possibility of this combination was established by artificial catheter induced right bundle branch block[3] In contrast to the loops resulting from total excitation via a left sided bypass the loops of left sided bypass with right bundle branch block display a distinct right anterior terminal appendage as in the usual forms of right bundle branch block described in an earlier section

Of great theoretical interest are those cases in which bundle branch block appears to exist in the same ventricle exhibiting the pre excitation A reasonable explanation seems to exist for Type B W P W of the posterior entrance type with coexistent right bundle branch block Here it seems possible that the posterior entrance leads to activation of the left ventricle via the fascicular system prior to activation of the right ventricle which in turn is aberrant because of the right

horizontal plane with a decrease in duration of the anterior P forces and an X axis intercept (crossing point from anterior to posterior) distinctly less than in the normal or in the patient with right atrial hypertrophy [2,5]

Recording of P loops in most clinical laboratories requires very careful attention to skin preparation electrode placement, respiratory phase of recording careful grounding of patient and equipment high amplification and use of one of the techniques to eliminate QRS and T data

Zoneraich and Zoneraich [88] have opened a new area for vectorcardiographic investigation with their concept of intra atrial conduction disturbances They have properly pointed out the parallel between the ventricular fascicular conducting system and the very similar internodal connections which join the SA node to the AV node and which pass through the atria They used extremely high amplification (300 mm per millivolt) and high frequency recording Using such technology to record normal P loops confirmed the location of the maximum vector as left inferior and posterior as described by other workers and also confirmed the previously observed normal rotation of the P loop as counterclockwise in the frontal and horizontal planes and clockwise in the right sagittal plane Two small notches were observed in normal patients one in the efferent and the other the afferent limb Maximum anterior or posterior voltages were confirmed as less than 0 1 millivolts Although the Zoneraichs described four different patterns for their patients with intra atrial conduction disturbances all patterns included many fine notches and bites These were frequently visible only in the vector display and not in the scalar presentations Such bites and notches were observed with and without left atrial dilatation as determined echocardiographically The Zoneraichs hypothesized that the bifid P wave scalar contour may well correspond to a lesion in the Bachmann bundle The authors comment [3] on the difficulties in assessing the separate contributions of conduction delay hypertrophy or dilatation to the observed P loop morphology

Vectorcardiographic studies of patients with atrial arrhythmias have been reported In low atrial rhythms either occurring spontaneously or pacemaker induced an expected shift of the maximum P vector occurs with a displacement to the right (left atrial rhythm) or to the left (right atrial rhythm) The rotation of the P loops in the frontal and horizontal planes varies according to the site of origin of the P loop and of the first atrium activated In the presence of inferior or low atrial rhythms no criteria are presently available for the identification of right or left atrial overload Vectorcardiography has been obtained in patients with atrial flutter [2,5,287] In 55 patients Zoneraich and co workers [83] described two vectorcardiographic patterns of flutter One, an elliptical smooth loop was found in 63% of patients with normal sized left atria and the second was a distorted flutter vectorcardiographic loop with many notches and bites This occurred in 67% of patients with enlarged left atria [3]

Following conversion of flutter patients to sinus rhythm notches and bites characteristic of intra atrial conduction delay were found in 62% of patients with enlarged left atria and in 43% of patients with normal sized atria by echocardiography Although the electrical activity in flutter is continuous masking the onset of activation correlations with prosthetic valve movement[285] seem to indicate that the onset of left atrial activation and contraction coincides with the rapid superiorly and posteriorly directed forces in the vectorcardiogram Right atrial activation then follows

Bartall and associates have studied the vectorcardiography of atrial fibrillation using timed loops Their criterion for detecting left atrial enlargement was a maximal VCG F wave exceeding 0 12 millivolts This was found in 25 of 38 subjects (66%) However only 10 of the 38 patients with atrial fibrillation had electrocardiographic F waves exceeding 0 1 millivolts in amplitude as measured in Lead V Of the 25 patients with increased F wave voltage by vectorcardiogram 21 had large left atrial dimensions by echocardiography Although the timed horizontal plane vectorcardiogram appears to be superior to Lead V of the electrocardiogram in atrial fibrillation in identifying enlargement of the left atrium additional explorations of this interesting area appear indicated

Wolff Parkinson White syndrome (references 2 to 16 290 to 303)

The vectorcardiography of QRS complexes in the W P W syndrome bears certain resemblances to the vectorcardiography of QRS complexes from ectopic ventricular sites In both types of loop the initial forces are inscribed with conduc

predicting not only the location of akinetic or dyskinetic segments after myocardial infarction but it has some value in predicting the extent of such dysfunction

11 Vectorcardiography has some of its greatest diagnostic value in patients with left bundle branch block Valuable clues to the presence of infarction in various areas as well as to right ventricular hypertrophy may be obtained

12 The vectorcardiography of pacemaker induced QRS complexes may strongly suggest the presence of underlying myocardial infarction A change in direction of the vectorial direction of the pacemaker spike itself may be a clue to wire fracture

13 High amplitude vectorcardiography of the P waves is a strong diagnostic tool in the recognition of right or left atrial overloads and is probably the best method available for the detection and evaluation of intra atrial conduction disorders

14 T loop vectorcardiography is of value in identifying unexpected rotations or speed of inscription which may frequently be a clue to ischemic disease in addition to identifying a secondary T abnormality as in bundle branch blocks

15 In children with the Wolff Parkinson White syndrome vectorcardiography provides valuable clues to the diagnosis of congenital heart disease

The author wishes to thank Mrs Esther Skolnik for invaluable help in reviewing the references and Mrs Marian Ango for her excellent secretarial work

REFERENCES

161 Pileggi, F Ebaid M Jatene A Bittencourt D Tranchesi J and Decourt L V Experimental vector cardiographic study of right bundle branch block Am J Cardiol 18 698 1966

162 Penaloza D Gamboa R and Sime E Experimental right bundle branch block in the normal human heart Electrocardiographic vectorcardiographic and hemodynamic observation Am J Cardiol 8 767 1961

163 Dodge H T and Grant R B Mechanisms of QRS complex prolongation in man Am J Med. 21 534 1956

164 Erickson R V Scher A M and Becker R A Ventricular excitation in experimental bundle branch block Circ Res 5 5 1957

165 Dickens J Maranhao V and Goldberg H Right bundle branch block A vectorcardiographic and electrocardiographic study of ventricular septal defect following open heart surgery Circulation 20 201 1959

166 Bristow J D Kassebaum D G Starr A and Griswold H E Observations on the occurrence of right bundle branch block following open repair of ventricular septal defects Circulation 22 836 1960

167 Scherlis L. and Lee Y C Right bundle branch block following open heart surgery Electrocardiographic and vectorcardiographic study Am J Cardiol. 8 780 19[illegible]

168 Scherlis L and Lee Y C Transient right bundle branch block An electrocardiographic and vectorcardiographic study Am J Cardiol. 11 173 1963

169 Baydar I D Walsh, T J and Massie E A vectorcardiographic study of right bundle branch block with the Frank lead system Am J Cardiol 15 185 196[illegible]

170 Doucet P Walsh T J and Massie E A vectorcardiographic study of right bundle branch block with the Frank lead system Am J Cardiol. 16 342, 1965

171 Rosenbaum M B Types of right bundle branch block and their clinical significance J Electrocardiol 1 221, 1968

172 Rosenbaum M B Elizari M V Lazzari, J O Nau, G J Levi R J., and Halpern M S Intraventricular trifascicular blocks Review of literature and classification AM HEART J 78 450 1969

173 Rosenbaum M B The hemiblocks Diagnostic criteria and clinical significance Mod Concepts Cardiovasc Dis 31 141 1970

174 Lemberg L Castellanos A J and Arcebal, A. G The vectorcardiogram in acute left anterior hemiblock, Am J Cardiol 28 483 1971

175 Kulbertus H Collignon P., and Humblet, L. Vectorcardiographic study of the QRS loop in patients with left anterior focal block AM HEART J 72 293 1970

176 Fernandez F Heller J Trevi, G Rabenou S Scebat, L. and Lenegre J The QRS loop in left anterior and posterior hemiblocks Vectorcardiographic study during selective coronary arteriography Am J Cardiol 29 337 1972

177 Okuma K ECG and VCG changes in experimental hemiblock and bifascicular block AM HEART J 92 473 1976

178 Benchimol A Bareto E C and Pedraza A The Frank vectorcardiogram in left anterior hemiblock, J Electrocardiol. 4 116 1971

179 Smith R F Harthorne J W and Sanders, C A. Vectorcardiographic changes during intracoronary injections Circulation 36 63 1967

180 Rosenbaum M B Elizari, M V Levi, R. J Nau G Pisani N., Lazzari J O and Halpern M D Five cases of intermittent left anterior hemiblock, Am J Cardiol 24 1 1969

181 Castellanos A Jr Chapunoff E Lemberg L, and Portillo B The vectorcardiogram in left posterior hemiblock. IN Vectorcardiography 2 Hoffman I ed, Amsterdam 1971 North Holland Publishing Co p 264

182 Schweitzer P Mellen H S and Rubenfire M Left posterior hemiblock J Electrocardiol. 4 204 1971

183 Brochet C R and Arnaud P Spatial Frank vectorcardiogram in left posterior fascicular block. Criteria and correlation with clinical and electrocardiographic data Br Heart J 39 176 1977

184 Benchimol, A and Desser K B The Frank vectorcardiogram in left posterior hemiblock, J Electrocardiol. 4 129 1971

185 Rasmussen K Quantitative vectorcardiographic crite-

bundle branch block Although some cases of type A pre excitation coexisting with apparent bundle branch block have been described this has never been reproduced experimentally and even the authors have no satisfactory explanation for the phenomenon Fortunately this last ... on is very rare

The diagnosis of myocardial infarction with ... Wolff Parkinson White syndrome is ... mely difficult if not impossible In one paper a patient with myocardial infarction had intermittent W P W syndrome The infarction abnormalities were totally obscured by the aberrant nature of the early forces when pre excitation was present although they were very visible with normal conduction

In one little-recognized area the recognition of congenital heart disease vectorcardiography may play a significant role in the presence of W P W Miller and Victorica have described the importance of the relationship between the delta and the main QRS axis in children suspected of congenital heart disease When these axes are more or less parallel congenital heart disease is usually absent For example a Type A pre excitation with an anterior QRS loop or a Type B with a posterior QRS loop would be more consistent with the absence of congenital heart disease However when these vectors are opposite in direction congenital heart disease was generally found Further the displacement of the major or mean QRS vector is generally oriented as expected for the appropriate ventricular hypertrophy Thus a posterior QRS vector in the presence of anterior delta vector suggests left ventricular hypertrophy In contrast right ventricular hypertrophy is more likely when the mean QRS is anterior despite a posterior delta vector in W P W Type B An interesting exception of this general rule is found in Ebstein s abnormality of the tricuspid valve Here Type B (posterior delta vector) is commonly found but the major QRS axis is also posterior In these patients the delta vector is also oriented in a superior direction

Indications for vectorcardiography

1 In the evaluation of clinically normal patients who have abnormal electrocardiograms especially apparently increased or decreased anterior forces the vectorcardiogram may be entirely normal comfirming the clinical impression

2 In the evaluation of chest pain problems with an apparently completely normal electrocardiogram a T loop study may disclose abnormal rotation of a wide but left and anterior horizontal loop This excellent sign of lateral ischemia may be completely hidden in the scalar record

3 Although high QRS voltage is better detected by scalar ECG criteria than by vector cardiographic or the orthogonal lead criteria the separation of right or left ventricular hypertrophy from combined hypertrophy is better accomplished by vectorcardiography

4 The vectorcardiogram is valuable in the differential diagnosis between pulmonary emphysema and anterior infarction

5 The vectorcardiogram is valuable in comfirming the presence of abnormally large anterior QRS forces and is particularly helpful in separating patients with right ventricular hypertrophy from patients with true dorsal infarction However it must be always remembered that anterior conduction delay Wolff Parkinson White Syndrome and hypertrophic and other cardiomyopathies may produce an identical picture Multiple myocardial infarctions are best recognized in the vectorcardiogram particularly when combined with bundle branch block or divisional block

6 The vectorcardiogram may also be of value in identifying the site of entrance of a bypass tract as free wall or septal in Wolff Parkinson White syndrome

7 Right ventricular hypertrophy is frequently easily diagnosed by vectorcardiography when it is only suspected in the conventional electrocardiogram

8 The diagnosis of right ventricular hypertrophy combined with right bundle branch block is frequently possible by vectorcardiography although care must be taken to avoid false positive diagnoses The combinations of right bundle branch block with inferior or superior divisional block are readily evident in the vectorcardiogram

9 With vectorcardiography it is possible to diagnose inferior infarction even in the presence of initial inferior forces which produce positive deflections in Leads 3 and aV_F of the scalar electrocardiogram Further it is possible to diagnose anterior infarction even in the presence of initially positive deflections in the right precordial leads

10 The vectorcardiogram may be of value in

220 Neuman J Blackaller J Tobin J R Jr Szanto P B and Gunnar R M The spatial vectorcardiogram in left bundle branch block Am J Cardiol 16 3;2 1965

221 Pietras R J Winslow E B J Boswell J Szanto P B and Gunnar R M The spatial vectorcardiogram in left bundle branch block Correlation of autopsy findings with the vectorcardiogram *in* Vectorcardiography 2 Hoffman I Hamby R and Glassman E eds Amsterdam and New York 1971 North Holland Publishing Company p 27"

222 Sanchez C Walsh T J and Massie E The vectorcardiogram in incomplete left bundle branch block Am J Cardiol 7 629 1961

223 Chou T C and Helm R A The diagnosis of right ventricular hypertrophy in the presence of left bundle branch block *in* Vectorcardiography 2 Hoffman I Hamby R I and Glassman E eds Amsterdam and New York 1971 North Holland Publishing Company p 289

224 Baydar I D Walsh T J and Massie E A vectorcardiographic study of right bundle branch block with the Frank lead system Clinical correlation in ventricular hypertrophy and chronic pulmonary disease Am J Cardiol 15 18; 1965

225 Miquel C Sodi Pallares D Cisneros F Pileggi F Medrano G A and Bisteni A Right bundle branch block and right ventricular hypertrophy Electrocardiographic and vectorcardiographic diagnosis Am J Cardiol 1 57 19;8

226 Fedor J M Walston A H Wagner G S and Starr J The vectorcardiogram in right bundle branch block Correlation with cardiac failure and pulmonary disease Circulation 53 926 1975

227 Chou T C Schwartz D and Kaplan S Vectorcardiographic diagnosis of right ventricular hypertrophy in the presence of right bundle branch block *in* Vectorcardiography 3 Hoffman I and Hamby R eds Amsterdam 19;(North Holland Publishing Co p 21

228 Krongrad E Hefler S E Bowman F O Jr Malm J R and Hoffman B F Further observations on the etiology of the right bundle branch block pattern following right ventriculotomy Circulation 50 1105 1974

229 Talbot S Kilpatrick D and Weeks B Vectorcardiographic features of ventricular extrasystoles correlated with conventional scalar electrocardiographic interpretation Br Heart J 40 883 1978

2;0 Sano T Hiroki I and Suzuki F The vectorcardiogram of ventricular premature beats An analysis of vectorcardiograms from 100 cases taken by Frank s method Jap Heart J 8 368 19(7

231 Castellan s A Jr Ortiz J Pastis N and Castillo C The vectorcardiogram of different pacemaker sites IN Vectorcardi graphy ? Hoffman I ed Amsterdam 1971 North Holland Publishing Company p 304

232 Castellanos A Jr Ghat ur A S Pastis N Myerburg R J and Berkovits B V The electrocardiogram and vectorcardi gram f ect pre ventricular beats Extrai des Acta Cardiologi a T 38 62 19"3

233 Klein M D Feldman C I Clark D L Flessas A I Ryan T J and Peura R A Vectorial characteristics of ventricular extrasystoles stimulated during cardiac catheterization J Electrocardiol 9 103 19 6

234 Gordon A J Vector analysis of the stimulus artifact in patients with endocardial pacemakers J Electrocardiol 4 91 1971

23; Zoneraich O and Zoneraich S Pacemaker vectorcardiography in patients with myocardial infarction and intraventricular conduction defects J Electrocardiol 4 1 1971

236 Castellanos A Jr Lemberg L Salhanick L and Berkovits B V Pacemaker vectorcardiography Am Heart J 75 6 1968

237 Castellanos A Jr Zoble R Procacci P M Myerburg R J and Berkovits B V St qR pattern New sign for diagnosis of anterior myocardial infarction during right ventricular pacing Br Heart J 35 110 1973

238 Burchell H B and Tuna N Initial vectors of ventricular premature beats and anterior fascicular conduction defects Eur J Cardiol 4 71 19 6

239 Zoneraich O Zoneraich S and Douglas A H The vectorcardiographic findings in patients with artificial pacemakers Dis Chest 53 436 1968

240 Kulbertus H E and Deleval Rutten F Vectorcardiographic study of QRS in patients with transvenous pacemakers and myocardial infarction J Electrocardiol 7 27 1974

241 Zoneraich S and Zoneraich O New vectorcardiographic findings in patients with myocardial infarction and artificial pacemakers *in* Vectorcardiography 3 I Hoffman and R I Hamby eds Amsterdam 19 6 North Holland Publishing Co pp 149

242 Zoneraich S Zoneraich O and Rhee J J Echocardiographic evaluation of septal motion in patients with artificial pacemakers Vectorcardiographic correlations Am Heart J 93 ;9(1977

243 Abildskov J A Millar K Burgess M J and Green L Characteristics of ventricular recovery as defined by the vectorcardiographic T loop Am J Cardiol 28 6 0 1971

244 Wajszczuk W J and Burch G E Analysis of the T loop in normal subjects of different ages Am J Cardiol 10 507 1962

245 Abildskov J A Burgess M J Millar K Wyatt R and Baule G The primary T wave—a new electrocardiographic waveform Am Heart J 81 24? 19 1

246 Harumi K Burgess M F and Abildskov J A A theoretic model of the T wave Circulation 34 6 19(6

247 Smithline F Hamby R I Hilsenrath J and Hoffman I The clockwise horizontal plane T loop A study of 73 patients J Electrocardiol 7 43 19 4

248 Castellanos A Jr Lemberg L Salhanick L and Gomez A The morphology of the ST T loop in healed myocardial infarction Dis Chest 50 113 1966

249 Murata K Kurihara H Matsushita S Ikeda M and Seki M Significance of T loop change in vectorcardiographic diagnosi of left ventricular hypertrophy Am Heart J 71 49 1967

2;0 Gray W and Bell H H Vectorcardiographic T loop analysis in ischemic heart disease Br Heart J 33 91 1971

ria for the differentiation between atrial septal defects of primum and secundum types J Electrocardiol 8 153 1975

186 Borkon A M Pieroni D R Varghese P J Ho C S and Rowe R D The superior QRS axis in ostium primum ASD A proposed mechanism AM HEART J 90 215 1975

187 Bashour T Hsu I Gorfinkel, H J Wickramesekaran R., and Rios, J C Atrioventricular and intraventricular conduction in hyperkalemia Am J Cardiol 35 199 1975

188 Nair M R. S and Duvernoy W F C Reversible fascicular block due to hyperkalemia Cardiovasc Med 10 985 1977

189 Lichstein E Chadda K D and Gupta P K Complete right bundle branch block with left axis deviation Significance of vectorcardiographic morphology AM HEART J 86 13 1973

190 Kulbertus, H., Collignon P., and Humblet L. Vectorcardiographic study of QRS loop in patients with left superior axis deviation and right bundle branch block Br Heart J 32 386 1970

191 Castellanos, A Jr Lemberg L. Ioannides G and Salhanick, L. The vectorcardiogram in right bundle branch block coexisting with left ventricular focal block, Am J Cardiol 18 705 1966

192 Castellanos A., Jr., and Lemberg L. Diagnosis of isolated and combined block in the bundle branches and the divisions of the left branch Circulation 43 971 1971

193 Benchimol, A., Desser K B., and Barreto E C Vectorcardiographic features of left anterior hemiblock combined with complete right bundle branch block J Electrocardiol 4 322 1971

194 Kulbertus H Collignon P and Humblet L Vectorcardiographic study of QRS loop in patients with left superior axis deviation and right bundle branch block Br Heart J 32 386 1971

195 Saltzman P Linn H and Pick A Right bundle branch block with left axis deviation Br Heart J 28 703 1966

196 Medrano G A and Brenes C P DeMicheli A and Sodi Pallares D Clinical electrocardiographic and vectorcardiographic diagnosis of the left anterior subdivision block isolated or associated with RBBB AM HEART J 83 447 1972

197 Medrano G A., Brenes, C P Micheli A and Sodi Pallares D Clinical electrocardiographic and vectorcardiographic diagnosis of left posterior subdivision block isolated or associated with RBBB AM HEART J 84 727 1972

198 Varriale P and Kennedy R J Right bundle branch block and left posterior fascicular block, Am J Cardiol 29 459 1972

199 Castellanos A Jr Chahine R A Chapunoff E Gomez J and Portillo B Diagnosis of left anterior hemiblock in the presence of inferior wall myocardial infarction Dis Chest 60 543 1971

200 Benchimol, A., and Desser K B Coexisting left anterior hemiblock and inferior wall myocardial infarction Vectorcardiographic features, Am J Cardiol 29 7 1972

201 Kulbertus H E Collignon P Humblet L. and Deleval Rutten F Left axis deviation in inferior infarction Vectorcardiographic recognition of concomitant left anterior hemiblock Dis Chest 60 362 1971

202 Kulbertus H E Electrocardiographic recognition of anterior infarction in left anterior fascicular block A diagnostic challenge Dis Chest 62 91 1972

203 Castellanos, A., Chapunoff E Castillo C A., Arcebal, A. G., and Lemberg L. The vectorcardiogram in left posterior hemiblock associated with inferior wall myocardial infarction Dis Chest 61 221 1972

204 Castellanos A Jr Diagnosis of left anterior hemiblock and left posterior hemiblock in the presence of inferior wall myocardial infarction Bull. N Y Acad Med 47 973 1971

205 Wagner R and Rosenbaum M B Transient left posterior hemiblock Association with acute lateral myocardial infarction Am J Cardiol. 21 558 1972

206 First S R Bayley R H and Bedford D R Peri infarction block Circulation 2 31 1950

207 Grant R. P Peri infarction block Progr Cardiovasc Dis. 2 237 1959

208 Mayer J W Castellanos A Jr and Lemberg L. The spatial vectorcardiogram in peri infarction block, Am J Cardiol 11 613 1963

209 Castellanos, A Jr and Lemberg L. Post infarction conduction disturbances, in Hoffman, I and Taymor R. C eds., Vectorcardiography 1965 Amsterdam 1966 Amsterdam North Holland Publishing Co p 219

210 Doucet P Walsh T J., and Massie E Vectorcardiographic study of right bundle branch block with the Frank lead system Clinical correlation in myocardial infarction Am J Cardiol 16 34 1965

211 Goldman M J and Pipberger H V Analysis of the orthogonal electrocardiogram and vectorcardiogram in ventricular conduction defects with and without myocardial infarction Circulation 39 243 1969

212 Bisteni, A Medrano G A De Micheli, A., and Sodi Pallares D Experimental myocardial infarction in the presense of bundle branch block, in Hoffman I ed Vectorcardiography 1965 Amsterdam 1966 North Holland Publishing Co p 296

213 Scott R C Left bundle branch block A clinical assessment Part I AM HEART J 70 535 1965

214 Scott R C Left bundle branch block A clinical assessment Part II AM HEART J 70 691 1965

215 Luna R. and Jackson A The vectorcardiogram in left bundle branch block Am J Cardiol 7 638 1961

216 Wallace A G Estes, E H and McCall B W The vectorcardiographic findings in left bundle branch block A study using the Frank lead system AM HEART J 63 508 1962.

217 Frimpter G W., Scherr L. and Ogden D The spatial vectorcardiogram in complete left bundle branch block with special reference to the initial component AM HEART J 55 220 1958

218 DePasquale N and Burch, G E The spatial vectorcardiogram in left bundle branch block and myocardial infarction with autopsy studies, Am J Med 29 633 1960

219 Doucet P., Walsh, T J., and Massie E A vectorcardiographic and electrocardiographic study of left bundle branch block with myocardial infarction, Am. J Cardiol. 17 171 1966

ultrasound vectorcardiographic and phonocardiographic findings Circulation 45 1206 1972
286 MacLean D Emslie Smith D and Lowe K G Spatial atrial vectorcardiogram in naturally occurring atrial flutter in man Br Heart J 35 817 1973
287 Cohen S I Koh D Lau S H Rosen K M and Damató A N P loops during common and uncommon atrial flutter in man Br Heart J 39 173 1977
288 Zoneraich O and Zoneraich S Intraatrial conduction disturbances Vectorcardiographic patterns Am J Cardiol 37 736 1976
289 Bartall H Desser K B Benchimol A and Massey B J Assessment of echocardiographic left atrial enlargement in patients with atrial fibrillation An electrovectorcardiographic study J Electrocardiol 11 269 1978
290 Bleifer S Kahn M Grishman A and Donoso E Wolff Parkinson White syndrome A vectorcardiographic-electrocardiographic and clinical study Am J Cardiol 4 321 1959
291 Chung K Y Walsh T J and Massie E Wolff Parkinson White syndrome AM HEART J 69 116 1965
292 Tranchesi J Guimaraes A C Teixeria V and Pillegi F Vectorial interpretation of the ventricular complex in Wolff Parkinson White syndrome Am J Cardiol 4 334 1959
293 Gamboa R Penaloza D and Banchero N The role of the right and left ventricles in the ventricular pre excitation (WPW) syndrome *An experimental study in* man Am J Cardiol 10 650 1962
294 Castellanos A Jr Mayer J W and Lemberg L The electrocardiogram and vectorcardiogram in Wolff Parkinson White syndrome associated with bundle branch block Am J Cardiol 10 657 1962
295 Verani M S Baron H and Maia I G Myocardial infarction associated with Wolff Parkinson White syndrome AM HEART J 83 684 1972
296 Lowe K G Emslie Smith D Ward C and Watson H Classification of ventricular pre-excitation Vectorcardiographic study Br Heart J 37 9 1975
297 Castellanos A Jr Lemberg L and Claxton B W Wolff Parkinson White syndrome Generalities, Dis Chest 65 307 1974
298 Castellanos A Jr Agha A S Portillo B and Myerburg R J Usefulness of vectorcardiography combined with His bundle recordings and cardiac pacing in the evaluation of the pre excitation (Wolff Parkinson White) syndrome Am J Cardiol 30 6?3 19?2
299 Tonkin A M Wagner G S Gallagher J J Cope G D Kasell J and Wallace A G Initial forces of ventricular depolarization in the Wolff Parkinson White syndrome Analysis based upon localization of the accessory pathway by epicardial mapping Circulation 52 1030 1975
300 Varriale P Alfenito J and Kennedy R J The simultaneous occurrence of ventricular pre-excitation left bundle branch block and delayed A V conduction AM HEART J 71 803 1966
301 Portillo B New electrovectorcardiographic concepts of the Wolff Parkinson White syndrome *in* Vectorcardiography 2 Hoffman I ed Amsterdam 1971 North Holland Publishing Co p 319
302 Miller B L and Victorica B E The vectorcardiogram of the Wolff Parkinson White syndrome in infancy and childhood *in* Vectorcardiography 2 Hoffman I ed Amsterdam 1971 North Holland Publishing Co p 597
303 Miller B L and Victorica B E Wolff Parkinson White syndrome in infants and children *in* Vectorcardiography 3 Hoffman I and Hamby R I eds Amsterdam 1976 North Holland Publishing Co p 137

251 Rubler S Hoffman I Franklin W D and Taymor R C The T loop in right bundle branch block AM HEART J 76 217 1968

? Castellanos A Jr Lemberg L and Salhanick L Programmed vectorcardiography The ST T loop in the horizontal plane AM HEART J 75 260 1968

253 Chou T C Co P and Helm R A Vectorcardiographic analysis of T wave inversion in the right precordial leads, AM HEART J 78 75 1969

254 Abdulla H M Dicovsky C and Zimmerman H A Morphologic features of the vectorcardiographic T loop in arteriosclerotic heart disease Am J Cardiol 24 18 1969

255 Castellanos, A Jr Salhanick L Lemberg L and Cohen R The T loop in normal children Am J Cardiol 16 336 1965

256 Gosselin A Lemberg L and Castellanos A Jr The T loop in congenital heart disease I Right ventricular overloadings Circulation 28 728 1963

257 Karni, H The TsE loop in myocardial lesions AM HEART J 52 867 1956

258 Chou T C Helm R A and Lach R The significance of a wide TsE loop Circulation 30 400 1964

259 Harumi K Mashima S Satao C Yamia Y, and Ueda H A study on the direction of inscription of the vectorcardiographic T loop in left and right ventricular hypertrophy Jap Heart J 4 486 1963

260 Castellanos, A Jr and Lemberg L The T loop in ventricular enlargements in congenital heart disease *in* Vectorcardiography 1965 Hoffman I and Taymor R C eds Amsterdam 1966 North Holland Publishing Co p 169

261 Hamby R I Hoffman I and Glassman E The T loop in right ventricular hypertrophy Dis. Chest 55 105 1969

262 McCaughan D Primeau R E and Littman D T wave changes in mitral stenosis Am J Cardiol 20 666 1967

263 Isaacs J H Mills H and Cole S The post exercise T loop The sequence of T loop changes in advanced angina ischemic heart disease *in* Vectorcardiography 2 Hoffman I Ed Amsterdam 1971 North Holland Publishing Co p 670

264 Kuo C S and Surawicz B Relationship of trans membrane action potential form to the T wave and T loop *in* Vectorcardiography 3 I Hoffman and R I Hamby eds Amsterdam 1976 Elsevier North Holland Publishing Co p 67

265 *Bizarro R O O'Brien P C Titus J L and Smith R* E Vectorcardiographic identification of myocardial scar A discriminative study with automatically processed vectorcardiographic information J Electrocardiol 11 273 1978

266 Kilpatrick D Exercise vectorcardiography in diagnosis of ischemic heart disease Lancet 2 33? 1976

267 Suzuki K and Toyama S A relation between the abnormal T loop and the exercise test J Electrocardiol 7 347 1974

268 Isaacs, J H Wilburne M Mills H Kuhn R Cole S L and Stein H The ischemic T loop during and following exercise—A vector-electrocardiographic (VECG) study J Electrocardiol 1 57 1968

269 Scheuer J Kahn M Bleifer S Donoso E and Grishman A The atrial vectorcardiogram in health *and disease* AM HEART J *60 33 1960*

270 Haywood L J, and Selvester R H Analysis of right and left atrial vectorcardiograms Timed records of 100 normal patients Circulation 33 577 1966

271 Selvester R H and Haywood L J High gain and high frequency atrial vectorcardiograms in normal subjects and in patients with atrial enlargement Am. J Cardiol 24 8017 1969

272 Giles T D Quiroz A C Sanchez G and Burch G E The influence of recording technique on the normal atrial vectorcardiogram Am J Cardiol 26 165 1970

273 Ishikawa K Kini P M and Pipberger H V P wave analysis in 2464 orthogonal electrocardiograms from normal subjects and patients with atrial overload Circulation 48 565 1973

274 Selvester R H and Pearson R H High gain averaged atrial vectorcardiograms in vectorcardiography 2 I Hoffman ed Amsterdam 1971 North Holland Publishing Co p 689

275 Duchosal P W Odier J and Boufas D The vector cardiogram of the P wave *in* Vectorcardiography 2 I Hoffman ed Amsterdam 1971 North Holland Publishing Co p 697

276 Brody D A, Cox J W McEachran A B Giles H and Ruesta V J Spatial parameters and shape factors of the normal atrial vectorcardiogram and its scalar components, Circulation 39 229 1969

277 Benchimol A Desser K H Tio S and Massey B J Vectorcardiographic diagnosis of atrial hypertrophy *in* Vectorcardiography 3 I Hoffman and R I Hamby eds. Amsterdam, 19 6 North Holland Publishing Co p 75

278 Benchimol A and Pedraza A The timed Frank vectorcardiogram in the diagnosis of cardiac arrhythmias J Electrocardiol 2 363 1969

279 Piccolo E Nava A Furlanello F, Permutti, B and Volta S D Left atrial rhythm Vectorcardiographic study and electrophysiologic critical evaluation AM HEART J 80 11 1970

280 Alfenito J C Kennedy R J and Varriale P Atrial vectorcardiogram in left atrial rhythm Dis Chest 56 110 1969

281 Piccolo E Nava A and Dalla Volta S Inferior atrial rhythms Vectorcardiographic study and electrophysiologic considerations AM HEART J 82 468 1971

282 Lau S H *Cohen S I Stein E., Haft J I Rosen K* M and Damató A N P waves and P loops in coronary sinus and left atrial rhythms AM HEART J 79 201 1970

283 Zoneraich O Zoneraich S Rhee J J, and Jordan D Atrial flutter Electrocardiographic vectorcardiographic and echocardiographic correlation AM HEART J 95 286 19 8

284 Burch, G E Giles T D Shewey L L and Cook G W Idiopathic enlargement of the right atrium of adult onset Am J Cardiol. 30 87 1972

285 Alderman E L Rytand D A Crow R S Finegan R E and Harrison D C Normal and prosthetic atrioventricular valve motion in atrial flutter Correlation of

tricular premature beats ventricular tachycardia and fibrillation as well as atrioventricular conduction disturbances have been reported to occur with phenothiazine therapy[5,10,13,14]

Kelly and co workers[5] reported fatal heart block and ventricular tachycardia in two patients treated with large doses of thioridazine and Desautels and associates[14] reported a case of non fatal ventricular tachycardia In 1965 Hollister and Kosek described six cases of sudden death in the absence of cardiac disease following phenothiazine treatment In all six patients a syncopal seizure episode was immediately followed by cardiorespiratory arrest In one case resuscitation was temporarily accomplished and irreversible ventricular fibrillation was documented on the electrocardiogram These patients were all receiving drug in the acceptable therapeutic dose range[12]

Lesstma and Koenig[15] reported fatal ventricular tachycardia in a 24 year old female treated with chlorpromazine thioridazine and stelazine Unexpected death in 12 patients receiving phenothiazine drugs was reported by Moore and Book[16] No adequate anatomic explanation for death was found in these cases and the ECGs were not available Death associated with ventricular arrhythmia was reported by Giles and Modlin[17] in a 19 year old male The fatal event followed repolarization changes seen on the ECG tracing and bouts of ventricular irritability[17]

Alexander and Nino[3] described tachycardia and left bundle branch block in a 36 year old asymptomatic man who was treated with phenothiazines However this patient received concomitant tricyclic antidepressant therapy which can also cause conduction disturbances[1] Fowler and colleagues in 1975[19] described electrocardiographic changes and cardiac arrhythmias in eight patients treated with psychotropic drugs Although most patients received more than one drug thioridazine seemed to be responsible for ventricular tachycardia in five of these eight patients and one of these episodes was fatal in a 35 year old female Supraventricular tachycardia was seen in one patient on chlorpromazine

The pathogenesis of phenothiazine induced rhythm disturbances is still unknown Prolongation of the Q T U interval has been demonstrated to be associated with ventricular arrhythmias.[19,20] Prolongation of the QT interval by phenothiazines suggests an increased duration of ventricular refractoriness and a low threshold for multiple ventricular responses and ventricular fibrillation[10,21] It is known that phenothiazines have a vagolytic effect and elevate plasma catecholamine levels which also may explain its arrhythmogenic effects

Lesions in the central nervous system particularly in the brainstem can affect the ECG repolarization process[23] The effect of phenothiazine on the ECG may be related to their profound action on the brainstem It is also possible tha the microscopic intramyocardial lesions describe in some patients treated with phenothiazine might be the basis for the abnormal electrocardio grams[5,4]

Although there is a slight risk of arrhythmi with therapeutic doses of phenothiazines the drugs have well documented antiarrhythmi effects[5,27] In experimental animals thioridazin caused a significant reduction of acetylcholine induced atrial fibrillation as well as a reversion o atrial fibrillation to normal sinus rhythm[7] I addition this agent caused a long lasting suppre sor action on ventricular ectopic tachycardi produced by two stage coronary ligation Th quinidine like properties of phenothiazines co tributes to the antiarrhythmic activity of the drugs

Hemodynamic effects of phenothiazines

A powerful vasodilator action has been demon strated with chlorpromazine[8] This vasodilato effect is caused by the blockade of peripher adrenergic receptors and a direct action of th drug on the smooth muscle of the arterial wal In addition the drug has a central nervous sy tem effect which contributes to its vasodilator activity Chlorpromazine has also been shown t have a direct depressant action on the myoca dium[1]

Effects on blood pressure

As a result of the peripheral vasodilatory an negative inotropic effects of phenothiazine hypotension is the most common side effect see in patients without congestive heart failure Afte several weeks of chronic therapy patients develo tolerance to the hypotensive effects of the dru and blood pressure returns to near normal leve However in some patients a certain degree o orthostatic hypotension persists This advers effect is more commonly seen with chlorproma zine and thioridazine than with the piperazin derivatives[1]

effects of phenothiazines

Elkayam M D
ıam Frishman M D *
Orange Calif and Bronx N Y

The phenothiazines are widely used drugs in medicine today In fact there are more an two dozen phenothiazine compounds being ed in medical practice [1] Chlorpromazine (Thorazine) and other phenothiazine derivatives are employed primarily in the treatment of patients with psychoses However they are also important antiemetic agents and some phenothiazine preparations are now being used for their antihistamine and analgesic effects as well

Experimental and clinical observations have demonstrated that phenothiazines have significant electrophysiologic and hemodynamic effects which may be of clinical importance The state of knowledge regarding the cardiovascular effects of phenothiazines will be reviewed

Electrophysiology and effects on the electrocardiogram

Experimental evaluations in animals demonstrated a significant effect of phenothiazines on the action potential of isolated atrial and ventricular muscle as well as Purkinje fibers Arita and Surawicz[3] showed that phenothiazines reduced membrane responsiveness by decreasing the maximal rate of rise of phase 0 of the action potential The psychotropic drugs also cause a decrease in the amplitude of phase 2 as well as a reduction in the rate dependent change in the duration of this phase Phase 3 was found to be prolonged following phenothiazine administration The electrophysiologic properties of phenothiazines are similar to those reported for quinidine [4] This explains the similar effects of phenothiazines and quinidine on the surface electrocardiogram

In man the earliest electrocardiographic change produced by phenothiazines is lengthening of the QT interval which is accompanied by widening blunting and notching of the T wave [5] These changes reflect the disturbances in ventricular repolarization and were found by Huston and Bell[6] in 53 of 106 (50%) hospitalized psychiatric patients receiving therapeutic doses of phenothiazines This study and others suggest that the T wave changes are benign Increasing doses of phenothiazines produce lowering and inversion of the T wave the ST segments are usually not affected but may be depressed [7] These drugs can prolong the PR and QRS intervals but have no effect on the P wave Electrocardiographic changes occur most commonly after the therapeutic administration of thioridazine are less pronounced after therapeutic doses of chlorpromazine and even less common after trifluoperazine [5,8]

The degree of electrocardiographic repolarization abnormality secondary to phenothiazine ingestion appears to be dose related 200 mg per day of thioridazine can sometimes be associated with detectable ECG changes while these changes occur more consistently with doses exceeding 800 mg per day [5,9]

Arrhythmogenic activity and antiarrhythmic effects of phenothiazines

Various arrhythmias have been attributed to the effects of phenothiazine therapy The arrhythmogenic effects of phenothiazines like quinidine can occur with therapeutic doses [1] Sinus tachycardia atrial fibrillation and flutter ven

From the Division of Cardiology Department of Medicine University of California Irvine Medical Center Orange Calif and the Division of Cardiology Department of Medicine Albert Einstein College of Medicine Bronx N Y

Supported in part by a grant No CHL-06?3 11 from the National Institutes of Health.

Received for publication Jan 6 1980

Reprint requests Uri Elkayam M D Division of Cardiology U C I Medical Center 101 City Drive South Orange Calif 92668

Dr Frishman is a Teaching Scholar of the American Heart Association

namic effects of intravenous chlorpromazine immediately after open heart surgery in 24 patients with high mean arterial pressures The average intravenous dose of 10 3 mg resulted in a significant decline in systemic blood pressure right and left atrial pressures and the pulmonary artery pressure There was no significant change in stroke volume however, cardiac output increased secondary to a significant rise in heart rate Chlorpromazine therapy caused a marked fall in both systemic and pulmonary vascular resistances

Hemodynamic effects on chlorpromazine in heart failure due to acute myocardial infarction

Significant beneficial effects on the hemodynamic profile were demonstrated by Elkayam and co workers[36] in 12 patients with acute myocardial infarction complicated by congestive heart failure The administration of 2 5 to 27 5 mg of chlorpromazine given as an intravenous bolus in increments of 2 5 mg repeated every 5 minutes was followed by a significant reduction in systemic vascular resistance and in mean capillary wedge pressure[36] (Figs 1 and 2) The drug also produced a marked elevation of cardiac output without a significant change in heart rate and mean stroke work index Although the administration of chlorpromazine resulted in a mean blood pressure fall of 18% the transmyocardial pressure gradient was not affected (Fig 2) The hemodynamic improvement was also accompanied by a dramatic increase in urine output Chlorpromazine therapy evoked a considerable degree of sedative effect and a decrement in motor activity in most of the patients

Cardiogenic shock

Dietzman and Lillehei[7] advocated phenoxybenzamine and chlorpromazine for treatment of cardiogenic shock They reported a reduction of the vasoactive response which results from an increase in circulating and tissue levels of catecholamines in patients with cardiogenic shock This vasodilatory effect of chlorpromazine mediated by the alpha adrenoceptor blockade of the pre and post capillary arteries and venules of the skin and viscera improved tissue perfusion and metabolism The authors concluded that this effect caused a decrease in morbidity in some patients

Data by Gulotta in 1970 and from Elkayam and co workers in 1977[36] also described the ber ficial effect of chlorpromazine in the low cardi output syndrome associated with open heart su gery and cardiogenic shock due to acute myoca dial infarction

Summary

Phenothiazines have significant electrophysi logic and cardiocirculatory effects The electr physiologic effect of these drugs is similar to th reported for quinidine Phenothiazines decrea the rate of rise of phase 0 of the action potenti decrease the duration and amplitude of phase and prolong phase 3 The surface ECG chan produced by phenothiazines are lengthenin the QTC interval ST T wave changes increas size of U waves and prolongation of the P interval The degree of repolarization abnormal ties secondary to phenothiazines seems to l dose related

Various arrhythmias have been attributed t the effect of phenothiazine therapy and nume ous cases of sudden death as a result of fat arrhythmia have been described Paradoxicall phenothiazines such as chlorpromazine and thio ridazine also have been shown to have significar antiarrhythmic properties Chlorpromazin shows a powerful vasodilatory effect which i caused by alpha adrenergic receptor blockade central action and a direct effect on the vascula wall In addition the drugs also have a direc depressant effect on the myocardium As a resul of peripheral vasodilatation and negative inotrop ic effects hypotension is the most commo adverse reaction of phenothiazines in patient with no evidence of congestive heart failure

Experimental studies have demonstrated si nificant reductions in systemic and pulmonary vascular resistance as well as systemic blood pressure following intravenous administration of chlorpromazine These hemodynamic changes were accompanied by significant increase in car diac output in one study and by no change in cardiac output in another study The vasodilatory effect of chlorpromazine resulted in increased renal and mesenteric blood flow and prolongation of survival time in dogs following hemorrhagic hypotension Chlorpromazine was found effective in relieving abnormal vascular tonus and improv ing the circulation in patients undergoing cardio-pulmonary bypass surgery In patients with myocardial infarction complicated by congestive

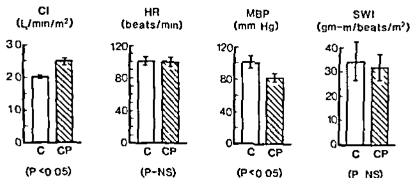


Fig 1 The effects of intravenous chlorpromazine *(CP)* vs baseline-no therapy *(C)* on cardiac index *(CI)* heart rate *(HR)* mean systemic blood pressure *(MBP)* and stroke work index *(SWI)* in 1? patients with congestive heart failure due to acute myocardial infarction The values are presented as means ± standard errors, *NS* = not significant (Reproduced by permission from Chest 72 6?3 6?7 1977)[14]

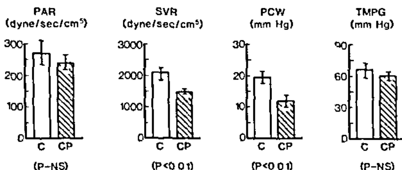


Fig 2 The mean effects of intravenous chlorpromazine *(CP)* vs baseline no therapy *(C)* on pulmonary arteriolar resistance *(PAR)* systemic vascular resistance *(SVR)* pulmonary capillary wedge pressure *(PCW)* and transmyocardial pressure gradient *(TMPG)*

Effect on systemic and pulmonary circulation

Goldberg and associates examined the effects of chlorpromazine on the pulmonary and systemic circulation in dogs The administration of an intravenous dose of 1 mg/kg produced a striking increase in cardiac output and a marked decrease in pulmonary vascular resistance The systemic vascular resistance and systemic blood pressure also fell significantly with no significant change seen in the heart rate

Similar experiments performed by Maxwell and co workers[1] demonstrated somewhat different results Using 1 mg/kg of chlorpromazine heart rate increased significantly and was accompanied by a marked reduction in systemic vascular resistance These changes were accompanied by a significant fall of systemic blood pressure and no change in cardiac output

Hemorrhagic shock

Inglis and associates have demonstrated prolongation of survival time in dogs treated with small intravenous doses of chlorpromazine following hemorrhagic hypotension Chlorpromazine increased renal blood flow and glomerular perfusion and significantly improved the renal medullary circulation[3] The beneficial effect of chlorpromazine on the renal circulation was accompanied by an improvement in cortical and medullary metabolism[33] and was associated with an increase in measurable diuresis during low levels of blood pressure The administration of chlorpromazine was also associated with a marked elevation of the mesenteric blood flow at an arterial blood pressure of 30 mm Hg

Cardiac surgery

Lemieux and colleagues[34] have demonstrated the effectiveness of chlorpromazine in relieving abnormal tonus of blood vessels in 30 patients undergoing cardiopulmonary bypass surgery The administration of the drug was associated with increased perfusion as indicated by an increase in percent oxygen saturation of venous blood and in urine output

Stinson and colleagues[35] studied the hemody

Limited pressure control to "optimum" levels *may reduce the rate of myocardial infarction* in hypertensive subjects

For more than 20 years it has been clear that *therapeutic* reduction of the blood pressure in hypertensive subjects dramatically lessens their increased liability *to illness* and death from left ventricular failure renal damage *and hemor* rhagic stroke while failing to make any incontestable *impres sion upon their similarly heightened susceptibility to myocar* dial infarction and sudden cardiac death The general reaction to this seeming paradox has been *one of pained disbelief* followed by renewed determination to squeeze *the pressure* down still further After all close relationships can be demon strated between hypertension and premature *arteriovascular* degeneration involving the blood *supply to various other* organs Why should the coronaries be different? Such reason ing makes *the unjustified assumption* that the effects of pressure change within *the arteries* supplying the brain and kidney must be the same as those *created within the nutrient* circulation of the heart It also takes no account of the extent to which high *blood pressure* should be reduced Surprisingly little attention *has been paid to* this important question and still less to another that is *even more fundamental* What is the mechanism whereby hypertension increases the infarction rate?

It has long *been thought* to do so by favoring coronary atherogene is The doctrines of pressure normalization and *of early treatment* in the young rest upon this widespread belief Yet the best that can be said for it is that the Framingham *studies have* shown a rising parallel between hypertension and the clinical manifestations of coronary *heart disease* This association has been readily accepted as *proof that* hypertension plays a significant role in the patho *genic processes within the coronary vessel walls The inference is ill founded* High blood pressure tends to precipitate angina and *myocardial* infarction in the pre ence of pre existing coronary *atheroma* whatever its origins Rather is there good reason to accept Pickering s view that hypertension is lowly *correlated* with coronary atheroma in this differing from the rest *of the arterial* irculation no doubt for the reason that the structural and *functional characteristics* of the heart are themselves unique In an angiographic assessment of risk *factors for atheroma* in 1'3 patients with and without coro nary *atheroma* the vessels being accounted as normal moderately or severely atherosclerotic Frick and his col leagues *found th t* the difference in the prevalence of *hypertension d d not* reach statistical significance in any comparison between *the groups*

In a pathological study of patients dying of congestive heart *failure Davis and* Klainer found marked coronary artery disease in 23 out of 2, *patients without hypertension* and in only 26 out of 49 patients with hypertension Later Harrison and Wood concluded that the coronary arteries vary sharply between hypertensive and ischaemic cases in the former they are large with smooth bores in the latter they are narrow frequently occluded Progression studies in coronary an raphy and experimental physiology [1] have pointed t same conclusion

There remains however a second possibility Mc *research has indicated that there may be important rela* ships between hypertension mental and physical stress, ticularly isometric stress sympathetic over activity e catecholamine circulation and potentially lethal ca arrhythmias [1, 4] This work is interesting in the context observation made by Berglund and colleagues In an ana of the rate of nonfatal myocardial infarction sustaine hypertensive patients under treatment as compared with in controls they noted that a significant benefit from pre reduction occurred early and continued throughout fo up So swift a response suggests the preemption of infar threatened by a precipitating rather than by a long factor A surge of very high pressure could be such a fa

It may be then that hypertension increases the ra infarction and sudden cardiac death largely by the occas precipitation of these events rather than by any signif influence upon coronary pathogenesis But if this be so has beta blockade with its promise of cardioprotection brought no clearly recognizable improvement? A recent s has suggested a po sible answer to this question

In a survey of middle aged severe essential hypert subjects most of them male followed under treatment o mean period of more than six years the final obse diastolic pressures (F D P s) as last recorded before moment of infarction or its avoidance in the patients who *suffered first myocardial infarction* were compared with in the patients who had avoided it There were no statist ly significant differences between the two groups in the n values for the other main coronary heart disease (C H D) factors But the relative risk of myocardial infarction sudden cardiac death in the patients with F D P reduce $<$ 90 mm Hg (Phase IV) was more than five times gre than that in the patients with F D P in the range of *100* mm Hg (P $<$ 0 01) the difference tailin off with F D about 110 to 114 mm Hg (Table I) This bimodality further illustrated by incidence comparisons between three major ranges of F D P —76 to 91 mm Hg 95 to 109 Hg and 110 to 140 mm Hg The ratios of patients infarctions to numbers *in each range* were respectively 10 of 41 4 out of 58 and 15 out of 70 Only in those whose F levels remained above 120 mm Hg did a clearly increased of infarction begin to reappear Other arteriovascular com cations were somewhat less than expected *from* patients under treatment despite relatively modest ind falls in many of them

Moreover in those who had developed an infarct

0002 8703/80/090402 + 03$00 30/0 © 1980 The C V Mosby

eart failure intravenous administration of ılorpromazine caused significant hemodynamic nprovement and a considerable degree of seda on The drug was found effective in reducing the asoactive response in patients with cardiogenic ıock which resulted in improved tissue perfusion nd metabolism

EFERENCES

1 Goodman L S and Gilman A The Pharmacological Basis of Therapeutics, 5th edition New York 1975 Macmillan Publishing Co Inc pp 157 166
2 Hollander P B and Cain R M Effects of thioridazine on transmembrane potential and contractile characteristics of guinea pig hearts Eur J Pharmacol 16 129 1971
3 Arita M and Surawicz B Electrophysiologic effects of phenothiazines on canine cardiac fibers J Pharmacol Exp Ther 184 619 1973
4 Hollander P B and Besch, H R An electropharmacological comparison between quinidine and dihydroquinidine on isolated rat atria Arch Int Pharmacodyn 178 407 1969
5 Kelly H G Fay J E and Laverty S G Thioridazine hydrochloride (mellaril) Its effect on the ECG and a report of two fatalities with ECG abnormalities Can Med. Assoc J 89 546 1963
6 Huston J R., and Bell G E The effect of thioridazine hydrochloride and chlorpromazine on the electrocardiogram J.A M A 198 16 1966
7 Wendkos L and Kosek, J C Sudden death during treatment with phenothiazine derivatives J.A M A 192 93 1965
8 Ban T A and St -Jean A The effect of phenothiazines on the electrocardiogram Can Med Assoc J 91 537 1964
9 Wendkos M H The significance of electrocardiographic changes produced by thioridazine J New Drugs Vol 3 and 4 322 1964
10 Surawicz B and Lasseter K C Effect of drugs on the electrocardiogram Progr Cardiovasc Dis 13 6 1970
11 Arita M and Mashiba H Effects of phenothiazine and propranolol on ECG Jap Circ J 34 391 1970
12 Hollister L E and Kosek J C Sudden death during treatment with phenothiazine derivatives J A M.A 192 1035 1965
13 Alexander C S and Nino A Cardiovascular complications in young patients taking psychotropic drugs. A preliminary report AM HEART J 78 757 1969
14 Desautels S Filteau C and St -Jean A Ventricular tachycardia associated with administration of thioridazine hydrochloride (Mellaril) Can Med Assoc J 90 1030 1964
15 Lesstma J E and Koenig K L Sudden death and phenothiazines Arch. Gen Psychiatry 18 137 1968
16 Moore M T and Book, M H Sudden death in phenothiazine therapy Psychiatr Q 44 389 1970
17 Giles, T D and Modlin R K Death associated with ventricular arrhythmia and thioridazine hydrochloride J.A.M.A 205 108 1968
18 Elkayam U Weinberg D and Frishman W Cardiovascular complication of desipramine overdosage. Cardiovasc Med 4 7, 1979
19 Fowler N O McCall D Chou T., Holmes, J C and Hamenson I B Electrocardiographic changes and cardiac arrhythmias in patients receiving psychotropic drugs Am J Cardiol 37 223 1976
20 James, T N QT prolongation and sudden death Mod Concepts Cardiovasc Dis 38 35 1969
21 Han J., Garcia De Jalon P D., and Moe G K. Fibrillation threshold of premature ventricular responses Circ Res 18 18 1966
22 Dietzman R H and Lillehei, R C The treatment of cardiogenic shock. Part IV The use of phenoxybenzamine and chlorpromazine AM HEART J 75 136 1968
23 Hugenholtz P G Electrocardiographic abnormalities in cerebral disorders Report of six cases and review of the literature AM HEART J 63 451 1962
24 Richardson H L Granpner K E., and Richardson M E Intramyocardial lesions in patients dying suddenly and unexpectedly J.A M.A 195 254 1966
25 Arora R B and Madan B R Chlorpromazine in experimental auricular flutter Indian J Physiol Allied Sci. 9 171 1955
26 Arora R. B., and Madan B R Chlorpromazine in experimental cardiac arrhythmias J Indian Med Assoc 26 262 1956
27 Madan B R., and Pendse V K Antiarrhythmic activity of thioridazine hydrochloride (mellaril) Am. J Cardiol. 11 78 1963
28 Poster C A. O'Mullane E J Gaskell, P and Church ill Davidson H C Chlorpromazine—A study of its action on the circulation in man Lancet 267 614 1954
29 Goldberg S J Linde L M Wolfe R R., Griswold W., and Momma K. The effects of meperidine promethazine and chlorpromazine on pulmonary and systemic circulation AM HEART J 77 214 1969
30 Maxwell G M Rowe G G Castillo C., Schuster B., White D H and Crumpton C W Hemodynamic effects of chlorpromazine including studies of cardiac work and coronary blood flow Anesthesiology 19 64 1958
31 Inglis F G Hampson L G., and Gurd, F N Therapeutic effects of chlorpromazine on experimental hemorrhagic shock Surg Forum 8 14 1958
32 Savlov E D and Regelson W Diuresis in hemorrhagic hypotension Surg Forum 7 40 1957
33 Murphy G P., Benson D W and Schirmer H. K A Renal response to chlorpromazine in hemorrhagic hypotension hemodynamic and metabolic changes and adrenolytic effects in dogs Ann Surg 164 867 1966
34 Lemieux M., Tice D A. Reed G E., and Clauss R H Chlorpromazine Adjunct to physiologic perfusion J Thorac Cardiovasc Surg 53 445 1967
35 Stinson E B Holloway E L Derby G., Oyer P E Hollingsworth J., Griepp R B., and Harrison D C Comparative hemodynamic responses to chlorpromazine nitroprusside nitroglycerin and trimethaphan immediately after open heart operations Circulation 51 and 52(Suppl.I) 26 1975
36 Elkayam U., Rotmensch, H H., Terdiman, R., Geller E., and Lanado S Hemodynamic effects of chlorpromazine in patients with acute myocardial infarction and pump failure Chest 72 623 1977
37 Gulotta, S J Chlorpromazine in the treatment of cardiogenic shock, AM HEART J 80 570 1970

artery disease a clinical arteriographic study Br Heart J 35 867 1973

11 Caro C G Transport of C-4 cholesterol between intra luminal serum and artery wall in isolated dog common carotid J Physiol—Proceedings of the Physiological Society 233 37 1973

12 Caro C G Personal communication 1976

13 Taylor S H Hypertension—its nature and treatment Ciba 269 1974

14 Ewing D J Irving J B Kerr F and Kirby B J Static exercise in untreated systemic hypertension Br Heart J 35 413 1973

15 Atkins, J M Matthews O A Blomquist C G and Mullins C B Incidence of arrhythmias induced by isometric and dynamic exercise Br Heart J 38 465 1976

16 Berglund G Sannerstedt R Andersson O Wedel H Wilhelmsen L Hansson L Silverstsson R and Wilk strand J Coronary heart disease after treatment of hypertension Lancet 1 1 1978

17 Stewart I McD G Relation of reduction in pressure to first myocardial infarction in patients receiving treat ment for severe hypertension Lancet 33 861 1979

18 Beevers D G Fairman M J Hamilton M and Harpur J E Antihypertensive treatment and the course of established cerebro-vascular disease Lancet 1 1407 1973

19 Berglund G Coronary heart disease after treatment of hypertension Lancet 1 114, 1978

20 Crawford T and Crawford M O Prevalence and pathological changes of ischaemic heart-disease in a hard water and in a soft water area Lancet 1 229 1967

21 Smith A J Drug treatment of hypertension, Br J Hosp Med. 11 533 1974

22 Lovegrove T Hypertension and myocardial infarction. Br Med J 2 2,9 1974

23 Stewart I McD G Optimised blood pressure Lancet 2 34 1979

24 Stewart I McD G New prospects in the treatment of hypertension Lancet 2 753 1957

Exercise and recurrence of myocardial infarction

The hypothesis that vigorous exercise rehabilitation is of benefit to patients following myocardial infarction is current ly being tested in Southern Ontario using a stratified ran domized controlled trial To date 50 of the 751 patients have been followed to the point of reinfarction and the resultant data has now been analyzed seeking clues to those individuals with an above average risk of a further coronary event

The most striking feature of this survey is the similarity of patients who infarct and those who do not' While the Southern Ontario multicenter sample included some individu als who had a slow progressive extension of their disease in *many individuals the second infarction (like the first)* occurred with little clinical or physiological warning This may reflect the nature of patients referred for exercise reha bilitation all were by selection under 54 years of age while the exercise program may have attracted cases with a relati ely mild initial episode and/or a fairly complete restoration of myocardial function

The only clinical clue to the likelihood of reinfarction gained from the patient s initial records was a history of multiple infarctions. Characteristics of the initial attack (symptomatology ECG changes enzyme changes cardiac arrest dysrhythmia and minimum systolic blood pressure) did not modify subsequent prognosis Presumably residual myocardial function is more crucial than the characteristics of the previous acute episode The referral process and criteria of admission to the multicenter trial may also have sorted out a relatively uniform type of patient suited to exercise with an infarct of less than average severity

The most important adverse finding on admission to the trial is exercise non compliance Total drop-outs have a risk of recurrence more than 20 times the average and limited exercise participation also increases risk by a factor of at least five Is this because advanced disease *and* poor myocardial function keeps some patients from performing the prescribed exercise? Residual disability shortness of breath and angina all increase the chances of recurrence but *nevertheless cardiac* problems are rarely cited as a reason for non compliance It is possible that those who fail to exercise are missing a therapeutic benefit of vigorous exercise but this again is doubtful since the figures from Southern Ontario and other trials to date suggest no advantage of high intensity exercise relative to *homeopathic* recreation or inactivity The most probable explanation is that exercise non compliance is serving as a marker of a generally adverse life style Many studies have shown the linkage between poor exercise compliance persistent smoking and obesity Rechnitzer and colleagues (unpublished *data*) *have* also noted that a combination of Type B personality a blue-collar job and vigorous exercise yield a poor prognosis Finally the group with recurrent infarction shows an above-average proportion of subjects engaged in commerce with a deficit in professional and managerial work.

Signs of a poor prognosis include cardiac enlargement aneurysm polyfocal ventricular premature beats exercise ST segmental depression and a serum cholesterol > 270 mg dl *The importance of deteriorating myocardial function is al*

Principal invest gat rs are G Andrew C Bu k D Cunningham N Jones, T Kavan gh, N Oldrid e J C Parker P Rechnit e S Sangal R. J Shephard, J Sutton nd M Yuhas Associat in estiga tors are F Berkman P Dem rs R Fowlis, P M los B Morton P Taylor and R Timming

0002 8 03/80/090404 + 02$00.20/0 © 1980 The C V Mosby Co

Table I Relative risks of myocardial infarction in ascending subgrades of FDP*

FDP (mm Hg)	Patients	Events	Relative risk	p
< 90	18	7	5 4	< 0 01
90 99	39	4	1 4	NS
100-109	4?	3	1 0	—
110-119	55	13	3 3	< 0 1
1?0+	15	2	1 9	NS

From Stewart, I McD G., Lancet 33 861 1979 Reproduced with permission.

F D P s ≤ 90 mm Hg the pressure falls were all markedly greater than in unaffected controls matched for C H D risk factors that included form of treatment age sex and established pretreatment diastolic pressure

These findings suggest that in severe middle aged hypertensive subjects attempts at normalization of the pressure may precipitate as many infarctions as it prevents perhaps cancelling out a lessened incidence at high levels a concept that is supported by an acknowledgment from Berglund and colleagues that in their study on the effects of treatment the percentage of well controlled patients after 2 years treatment was indeed low despite their lessened infarction rate compared with that of the untreated

All this constitutes a challenge to the popular concept of good control. But it can scarcely be accounted surprising Misled by mean values and persuaded by those who would have it that hypertension is a potent cause of coronary atheroma clinicians throughout the world have continued to pay lip service to the proposition that reduction of blood pressure to normal levels should diminish the incidence of myocardial infarction in hypertensive patients Yet there is no convincing evidence that hypertension significantly favors coronary atherogenesis nor that lowering systemic pressure can arrest it Certainly the prospect of longevity as shown by actuarial tables is improved by a blood pressure that has continued or possibly (as remains to be seen) has always been controlled at a normal level But this simple epidemiological appreciation takes no account either of the individual patient or of the site of the fatal lesion Some 30% of middle aged Englishmen and no doubt many more such men who have adopted the life styles of the Western type civilization whether hypertensi e or not already have advanced coronary artery disease often unsuspected[ ] It is easy to believe that severe contrived reductions in their systemic arterial pressure impinging fortuitously upon the constantly changing mechanisms of auto-regulation may sometimes lead to disastrous failures of coronary perfusion, perhaps with stasis and platelet aggregation the risk made all the greater by the diverse and frequently unpredictable modes of action of the hypotensive drugs concerned. Such combinations of drug and circumstance have already been shown to precipitate myocardial infarction in patients under close observation in hospital

For many reasons the clinical reduction of blood pressure is an imprecise exercise Even when aimed at levels well above normality " it may still occasionally overshoot the mark to a degree that threatens critical and possibly fatal, myocardial ischaemia Thus it may well be that in its treatment no less than in its natural history hypertension presents a dual threat of infarction and sudden cardiac death by precipitation of these events at each extremity of the pressure scale This threat should be avoidable in both its forms if "good control" be taken to imply not normality the standardized average for age and sex but a decrease in pressure sufficient to restrain hypertensive injury to target organs, including the heart while avoiding such hypotension as may set off infarction.

In 1957 it was suggested that "even a limited depression of the blood pressure could be as effective "as the most exacting control. " Today it would seem reasonable to conclude that at least in severe hypertensive subjects the policy should be one of reduction into an optimum range calculated as far as possible for the individual that is likely still to be considerably above that of normalization" after induced pressure falls of perhaps no more than about 22% or to a diastolic pressure of around 104 to 110 mm. Hg

I McD G Stewart M.D F.R.C.P
Department of Medicine
Victoria Hospital
Blackpool
England

REFERENCES

1 Yater W M Traum A H Brown W C., Fitzgerald R P Geisler M A., and Wilcox B B Coronary artery disease in men 18-39 years of age Report on eight hundred and sixty six cases, four hundred and fifty with necropsy examinations, AM HEART J 36 334 1948
2 Taguchi, J and Freis E D Partial reduction of blood pressure and prevention of complications in hypertension N Engl J Med 291 329 1974
3 MacGregor A M Diseases of the urinary system High blood pressure and renal disease Br Med. J 2 624 1977
4 Raftery E B Why beta blockers are my first line choice Modern Medicine Hypertension Supplement, 32 19 8
5 Kannel W B and Dawber T R Hypertension as an ingredient of a cardiovascular risk profile Br J Hosp Med. 11 508 1974
6 Pickering G W Antihypertensive Therapy Berlin 1966 Springer Verlag p 135
7 Davis, D and Klainer M J Studies in hypertensive heart disease IV Factors in the production of congestive failure AM HEART J 20 98 1940
8 Harrison C V and Wood, P Hypertensive and ischaemic heart disease a comparative clinical and pathological study Br Heart J 11 205 1949
9 Frick, M Dahlen G., Berg K., Valle M and Hekali, P Serum lipids in angiographically assessed coronary atherosclerosis Chest 73 62 1978
10 Gorlin R and Bemis, C E Progression of coronary

artery disease a clinical arteriographic study Br Heart J 35 867 1973
11 Caro C G Transport of C-4 cholesterol between intra luminal serum and artery wall in isolated dog common carotid J Physiol—Proceedings of the Physiological Society 233 37 1973
12 Caro C G Personal communication 1976
13 Taylor S H Hypertension—its nature and treatment Ciba 269 1974
14 Ewing D J Irving J B Kerr F and Kirby B J Static exercise in untreated systemic hypertension Br Heart J 35 413 1973
15 Atkins, J M., Matthews, O A Blomquist C G., and Mullins C B Incidence of arrhythmias induced by isometric and dynamic exercise Br Heart J 38 465 1976
16 Berglund G Sannerstedt R Andersson O Wedel, H Wilhelmsen L., Hansson L. Silverstsson R and Wilk strand J Coronary heart-disease after treatment of hypertension Lancet 1 1 1978
17 Stewart I McD G Relation of reduction in pressure to first myocardial infarction in patients receiving treatment for severe hypertension Lancet 33.861 1979
18 Beevers D G Fairman M J Hamilton M a. Harpur J E Antihypertensive treatment and the course of established cerebro-vascular disease, Lan. 1 1407 1973
19 Berglund G Coronary heart disease after treatm nt hypertension Lancet 1 1147 19 8
20 Crawford T and Crawford M O Prevalence a. pathological changes of ischaemic heart-disease in hard water and in a soft water area, Lancet 1 2 1967
21 Smith, A J Drug treatment of hypertension, Br Hosp Med. 11 533 1974
22 Lovegrove T Hypertension and myocardial infarcti Br Med J 2 279 1974
23 Stewart I McD G Optimised blood pressure Lan 2 34 1979
24 Stewart I McD G New prospects in the treatment hypertension Lancet 2 753 1957

Exercise and recurrence of myocardial infarction

The hypothesis that vigorous exercise rehabilitation is of benefit to patients following myocardial infarction is currently being tested in Southern Ontario using a stratified randomized controlled trial To date 50 of the 751 patients have been followed to the point of reinfarction and the resultant data has now been analyzed seeking clues to those individuals with an above average risk of a further coronary event

The most striking feature of this survey is the similarity of patients who infarct and those who do not[1] While the Southern Ontario multicenter sample included some individuals who had a slow progressive extension of their disease in many individuals the second infarction (like the first) occurred with little clinical or physiological warning This may reflect the nature of patients referred for exercise rehabilitation all were by selection under 54 years of age while the exercise program may have attracted cases with a relatively mild initial episode and/or a fairly complete restoration of myocardial function

The only clinical clue to the likelihood of reinfarction gained from the patient s initial records was a history of multiple infarctions Characteristics of the initial attack (symptomatology ECG changes enzyme changes cardiac arrest dysrhythmia and minimum systolic blood pressure) did not modify subsequent prognosis Presumably residual myocardial function is more crucial than the characteristics of the previous acute episode The referral process and criteria of admission to the multicenter trial may also have sorted o relatively uniform type of patient suited to exercise wit infarct of less than average severity

The most important adverse finding on admission to trial is exercise non compliance [2] Total drop-outs hav risk of recurrence more than 20 times the avera e limited exercise participation also increases risk by a facto at least five Is this because advanced disease and p myocardial function keeps some patients from performing prescribed exercise? Residual disability shortness of bre and angina all increase the chances of recurrence nevertheless cardiac problems are rarely cited as a reason non-compliance [3] It is possible that those who fail to exer are missing a therapeutic benefit of vigorous exercise but again is doubtful since the figures from Southern Onta and other trials to date suggest no advantage of h intensity exercise relative to homeopathic recreation or u tivity The most probable explanation is that exercise n compliance is serving as a "marker of a g nerally adv life-style Many studies have shown the linkage between p exercise compliance persistent smoking and obesity Rechnitzer and colleagues (unpublished data) have also no that a combination of "Type B" personality a blue-collar, and vigorous exercise yield a poor prognosis Finally the gr with recurrent infarction shows an above average proport of subjects engaged in commerce, with a deficit in professional and managerial work.

Signs of a poor prognosis include cardiac enlargemen aneurysm polyfocal ventricular premature beats, exercise T segmental depression and a serum cholesterol > ? 0 mg d The importance of deteriorating myocardial function is also

Principal investigators are G Andrew C Buck D Cunningham N Jones, T Kavanagh, N Oldridge J C Park r P Rechn tzer S Sangal, R. J Shephard, J Sutton and M Yuhasz. Associate in estiga tors are F Berkman, P Demers, R. Fowlis P Mil s B Morton P T ylor and R Timming

0002-8703/80/090404 + 02$00.20/0 © 1980 The C V Mosby Co

ested by the inability to develop a normal rise of systolic blood pressure during exercise. Nevertheless, physiological response to exercise does not show major differences in those who sustain reinfarction. Possible warnings include a low cardiac output relative to work rate, a widened arteriovenous oxygen difference, and poor matching of ventilation and perfusion. None of these indicators are very clear-cut, presumably because recurrent disease includes both cases of sudden ventricular dysrhythmia and individuals who develop progressive pump failure.

With the possible exception of exercise non-compliance, the ratios for the various warnings we have discussed are too low to be of great value in advising individual patients. The safety of exercise rehabilitation will thus continue to depend upon a cautious initial prescription of exercise, gradual progression, and temporary restriction of activity in the face of adverse symptoms.

Roy J. Shephard, M.D., Ph.D.
School of Physical and Health Education
University of Toronto
320 Huron Street
Toronto, Ontario
M5S 1A1
Canada

REFERENCES

1. Rechnitzer PA, Sangal S, Cunningham DA, Andrew G, Buck C, Jones NL, Kavanagh T, Parker JO, Shephard RJ, and Yuhasz MS: A controlled prospective study of the effect of endurance training on the recurrence rate of myocardial infarction. A description of the experimental design. Am J Epidemiol 120:358, 1975.
2. Shephard RJ: Recurrence of myocardial infarction in an exercising population. Br Heart J 42:133, 1979.
3. Shephard RJ, and Kavanagh T: Prognostic indices for ischemic heart disease patients enrolled in an exercise centered rehabilitation programme. Am J Cardiol 44:1250, 1979.
4. Shephard RJ, Corey P, and Kavanagh T: Exercise compliance and the prevention of a recurrence of myocardial infarction. Can J Appl Sports Sci 4:236, 1980.
5. Bruce RA, DeRouen T, Peterson DR, Irving JB, Chinn N, Blake B, and Hofer V: Non invasive predictors of sudden cardiac death in men with coronary heart disease. Predictive value of maximal stress testing. Am J Cardiol 39:833, 1977.
6. Oldridge N: Compliance of post myocardial infarction patients to exercise programs. Med Sci Sports 11:373, 1979.
7. Wilhelmsen L, Sanne H, Elmfeldt D, Grimby G, Tibblin G, and Wadel H: A controlled trial of physical training after myocardial infarction. Prev Medicine 4:491, 1975.
8. Kentala E: Physical fitness and feasibility of physical rehabilitation after myocardial infarction in men of working age. Ann Clin Res 4(Suppl. 9):1, 1972.
9. Massie JF, and Shephard RJ: Physiological and psychological effect of training. Med Sci Sports 3:110, 1971.
10. Sidney KH, and Shephard RJ: Frequency and intensity of exercise training for elderly subjects. Med Sci Sports 10:125, 1978.
11. Kavanagh T, and Shephard RJ: The immediate antecedents of myocardial infarction in active men. Can Med Assoc J 109:19, 1973.

Giant cell arteritis—a cardiological blind spot?

Few would disagree that the cardiologist has been faced with and has overcome several major challenges in his field during recent decades. One which remains and unfortunately appears to have been largely ignored is that presented by giant cell arteritis (GCA). Thus Paulley recently asked the question: "What, then, is happening to the bulk of these patients referred to cardiologists who, it seems, are either seeing this disorder and not diagnosing it or diagnosing it but not reporting it?" Our clinical experience, a survey of publications, and the lack of reference to GCA in major cardiological texts all suggest that the former situation is more prevalent. Indeed, with GCA, diagnostic delays or failures permeate well beyond the boundaries of cardiological practice and undoubtedly occur more frequently than is generally appreciated within every major subspecialty of internal medicine.

Although GCA may cause angina pectoris, myocardial infarction, aortic regurgitation, aortic dissection, congestive cardiac failure, perhaps pericarditis, and even simulate infective endocarditis, its prevalence in cardiological practice is unknown. Recognition that arteritis may be the underlying cause of these cardiac events during life is by no means easy, demanding a high index of suspicion and awareness of the deceptive natural history of the disease. Yet there are data indicating that GCA is by no means a rare disease, affecting more than one per cent of the elderly Caucasian population. The dominance, however, of atherosclerosis in the league of diseases in Western countries has generated complacency with regard to consideration of less commonly seen disorders such as this arteritis.

It has become increasingly apparent that GCA is a chronic disease of varying severity and fluctuating course extending over a few to as many as 10 to 15 years. While temporal arteritis is easily diagnosed, events such as unexplained anemia, pyrexia of undetermined origin, malaise, depression, or a negative laparotomy for possible malignancy, any of which may have occurred months or years earlier, are presentations to which the cardiological mind is not often attuned. Nevertheless, these may be the only clues indicating the true cause

0002-8703/80/090405 + 03$00.30/0 © 1980 The C. V. Mosby Co.

Effective coronary care and mortality rates

To the Editor

May I refer to your Editorial Home or hospital for myocardial infarction—who cares? This is based on the Nottingham study reported in 1978 I would like to point out the limitations of this study It was carried out over a four year period and covered a population of approximately 100 000 From the expected incidence of myocardial infarction some 1,200 cases would have been anticipated among that population over the four year period Two hundred and sixty four patients suspected of having a myocardial infarction were randomized However only 150 of these had a definite or probable myocardial infarction and were randomized to home or hospital treatment Thus of the patients likely to have had a myocardial infarction only 12 5% were randomized This is remarkable in that the Nottingham workers point out that one of the major defects of the Bristol study was the small proportion of patients who were randomized

From their study the Nottingham workers concluded that "For the majority of patients to whom a general practitioner is called because of suspected infarction hospital admission confers no clear advantage " Yet in their study over 40% of the patients with suspected myocardial infarction had contacted their doctor within one hour of the onset of symptoms and nearly 60% within two hours Nevertheless the average time from the onset of symptoms to the mobile team s arrival with the patient was three hours and a further two hours elapsed prior to randomization It may be concluded that in the Nottingham study there was a larger administrative delay than patient delay The authors record that during the time between the patient s call for help and the arrival of the mobile team 14 patients died presumably suddenly and from ventricular fibrillation A further seven patients developed ventricular fibrillation after arrival of the team yet only three of these seven survived six weeks Seventy three percent of the patients managed by the Belfast unit who developed ventricular fibrillation outside hospital after the mobile team s arrival survived to leave hospital The standard of coronary care received by the patients in Nottingham both outside and inside hospital must be questioned since it is reported that patients on admission to the coronary care unit come under the care of a general physician on duty that day The head of the unit considers his role to be that of an administrator and educator The junior doctors manning the mobile coronary care unit are drawn from the general medical units of the hospital

In the Editorial the authors state that "76% of patients seen by the team were suitable for care at home Yet among those patients with a final diagnosis of definite or probable myocardial infarction who were excluded from randomization the six week mortality rate was 37% No explanation for this very high mortality rate is given

The Nottingham data show the obvious If patients are seen late after the onset of symptoms the effect of coronary care will be minimal Despite the evidence from Belfast and Seattle Hampton and Nicholas conclude that mobile coronary care units as at present envisaged will not appreciably affect mortality from heart attacks This conclusi n dangerously erroneous and has already inhibited the develo ment of prehospital coronary care schemes in Britain sin apparently the policy of the Department of Health is based the Nottingham propaganda Sadly therefore there will co tinue to be 5 000 unnecessary deaths annually in the Unit Kingdom

A A J Adgey MD FRC
Consultant Cardiolog
Regional Medical Cardiology Cen
Royal Victoria Hosp
Belfast BT12 6BA Northern Irela

REFERENCES

1 Hill J D Hampton J R., and Mitchell J R A. Ho or hospital for myocardial infarction—who cares A HEART J 98 545 1979
2 Hill J D Hampton J R and Mitchell J R A randomised trial of home versus ho pital managem for patients with suspected myocardial infarction, La cet 1 837 1978
3 Colling A Carson P and Hampton J Home hospital care for coronary thrombosis? Br Med 1 1254 1978
4 Colling A Dellipiani A W Donaldson R I MacCormack P Teesside coronary survey an epid iological study of acute attacks of myocardial infarcti Br Med J 2 1169 1976
5 Mather H G Pearson N G Read K L Q Shaw B Steed G R Thorne M G Jones S Guerrier C Eraut C D McHugh P M Chowdhury N R Jafa M H and Wallace T J Acute myocardial infarcti Home and hospital treatment Br Med J 3 334 19
6 Hampton J R and Nicholas C Randomised trial mobile coronary care unit for emergency calls, Br M J 1 1118 1978
7 Editorial Ventricular fibrillation out ide hospital L cet 2 508 1979

Reply

To the Editor

Doctor Adgey is of course entitled to state her own opin on our published work but what she should not do is attempt to reanalyze our data in a way which could mi others May we suggest that your readers should scrutinize original paper[2] on which our Editorial was based They then form their own opinions and can judge for themselves validity of Doctor Adgey s comments

J R Hamp
Consultant Physic
Department of Medic
University Hosp
Queen s Medical Cen
The University of Nottingh
Nottingham NG7 2
Engla

areas in temporal arteritis Arch. Ophthalmol. 94 20 2 19 6
1 Gillanders L. A., Strachan R W., and Blair D W Temporal arteriography A new technique for the investigation of giant cell arteritis and polymyalgia rheumatica Ann Rheum Dis 28 267 1969
Sewell J R Allison D J., Tarin D and Hughes G R V Combined temporal arteriography and selective biopsy in suspected giant cell arteritis Ann Rheum Dis 39 1?4 1980
Kulvin S M Erythrocyte sedimentation rates in the elderly Arch Opthalmol 88 61? 19?
7 Hayes, G S and Stinson I N Erythrocyte sedimentation rate and age Arch Ophthalmol 94 939 19?6
18 Gibson I I J M The value of the erythrocyte sedimentation rate in the aged Gerontol. Clin 14 185 19?2
19 Clinicopathological Conference Two neurological cases Br Med J 1 ??? 19?9
20 Kansu T Corbett J J Savino P., and Schatz N J Giant cell arteritis with normal sedimentation rate Arch Neurol 34 624 19 ?
21 Wiggins W S Rollinson R D Schwartze M and Laster W Temporal arteritis with normal sedimentation rate South. Med J 71 1448 19?8
2? Cherry J E., and Pearce J M S Unusual variants in the presentation of temporal arteritis Postgrad Med J 56 88 1980

Of senile anemia

Old patients with or without active heart disease regularly with chronic anemia It is important that the general health of the patient with heart disease always be considered not only because associated diseases contribute to the patient s symptom complex but also because some associated diseases affect the heart directly and/or indirectly This is certainly true of anemia When the concentration of red cells and hemoglobin is low the oxygen transport buffer mechanisms, and other important functions of hemoglobin and erythrocytes are impaired and the myocardium suffers as a consequence

Heart disease is especially common in older people It is well to realize that many old people have chronic anemia for which the etiology remains unknown Even after extensive hematologic study with all available methods the cause is not established satisfactorily The anemia may vary from mild to severe Yet the use of all therapeutic measures and agents fails to modify it except for the temporary influence of transfusions. But transfusions can be dangerous in that they may precipitate congestive heart failure in people with heart disease when transfusions are not used properly and cautiously

This type of chronic anemia of "unknown" cause in old people may be called senile anemia " the anemia of old age the result of poor function of an old hemopoietic system Unless the anemia is severe and is contributing to the ill health or to the cardiac disease of the elderly patient it should be left alone After all, sluggish and relatively inactive old people do not need as much circulating blood or hemoglobin as young extremely active people do

George E Burch M.D
Tulane University School of Medicine
and Charity Ho pital of Louisiana
New Orleans La 70112

REFERENCES

1 Adler S S Anemia in the aged Causes and considerations Geriatrics 35 49 1980
2 Davison W Anemia in the elderly with pecial reference to iron deficiency Geront Clin 9 393 1967
3 Milne J S and Williamson J Hemoglobin hematocrit leukocyte count and blood grouping in older people *Geriatrics* 27 118 19?2

000?-8 03/80/090407 + 01$00 10/0 © 1980 The C V Mosby Co

Table I Effect of flow rate on percentage of NTG remaining after passage through polyvinyl chloride infusion set

Flow rate (ml/min)	Time (min)								
	zero	30	60	90	120	180	240	300	3[illegible]
0 25	22 7	30 6	36 5	40 2	44 4	48 6	52 3	–	55
0.50	42 6	52 8	57 6	63 9	65 1	69 0	72 2	73 8	76.
0 75	50 0	62 3	66 9	71 4	73.5	[illegible]7 2	79 ?	80 9	81
1 00	50 7	–	69 9	–	78 5	83 6	84 1	84 [illegible]	8 .

but too often we forget that there is something else between the patient and the container—a system that in this very case turns out to be more important!

John Ph A Branje
Bert Berghuis
Dept of Pharmacy
Sophia Ziekenhuis
Zwolle The Netherlands

REFERENCES

1 Cacace L G Harralson A and Clougherty T Stability of NTG AM HEART J 97 816 1979
2 Branje J Ph A., and Berghuis B Enige mededelingen omtrent intraveneuze nitroglycerine injecties Mededelingen van de Nederlandse Vereniging van Ziekenhuisapothekers 38 400 1979
3 Yap S K Rhodes C T and Fung H L. Factors affecting the kinetic assay of NTG in dosage forms Am J Hosp Pharm 32 1039 1975

Sex and the differential diagnosis of uncomplicated angina pectoris

To the Editor

In a recent publication from a widely respected epidemiological investigational team on the occasion of reporting an extraordinary high percentage of remission of angina pectoris cases first the validity of the acquisition of the anginal symptomatology was questioned and secondly a disturbing distribution between sexes of such patients emerged

The aim of this paper is not to deal either with the remission rate of this symptom complex or with its eventual significance The finding however of a 13% preponderance of women (N = 84) over men (N = 74) in a natural (unselected) population is in fact astounding and not only on theoretical, but also on practical grounds. It was therefore thought to be very constructive to expose briefly the findings of an investigation concerning this matter We evaluated with the HIP questionnaire for angina pectoris 200 consecutive cases addressed to us with the problem or recurring chest pain The following groups of cases were not included in the above 200 cases (1) cases with historical and or electrocardiographic documentation of old myocardial infarction (2) cases where the electrocardiographic and or enzymatic follow up was diagnostic of a re ent myocardial infarction (3) cases with valvular disease click syndrome cardiomyopathies (4) cases with bundle branch [illegible] k and (5) cases of recent administration of digitalis prep ration (The last two prerequisites were set because of a parallel study of the resting repolarizatio[illegible] the included cases)

Thus the consecutive studied cases consisted of 108 men 92 women The characterization of the chest pain compl[illegible] by the HIP questionnaire and other relevant parameters shown in Table I.

It can be seen from the table that the mean a e—as expected—was higher in cases with angina pectoris as [illegible] pared with cases of non anginal chest pain (and significa[illegible] so for men $p < 0\,01$) also SBP was higher in the same co[illegible] (and significantly so for women $p < 0\,05$) It is interesting to note the high occurrence of abnormal resting repolarization in cases with non anginal chest pain although it will not be discussed here The most important finding however was that the probability of a middle a ed person presenting with recurring chest pain to have angina pectoris is 0 38 (41 out of 108) for men and only 0 03 (3 out of 9?) for women Therefore angina pectoris is almost 12 times less frequent in women than in men of comparable a e This conclusion is in absolute contrast to the above mentioned findings (from the Framingham study)

It would be fruitful to speculat about this striking differ ence The whole evidence so far has been for a clear predom nance of male sex in Heberden s classical description of [illegible] cases of angina pectoris only three women were encountered In seven series on the subject (published between 19[illegible]0 a[illegible] 1959) and reviewed by Segal the ratio varied between ? 5 and seven men for one woman

Burch stated that angina pectoris was more common in men than in women Finally Friedberg mentioned a ratio of three to six men for each woman

One might argue that in an unselected population (such as that of the Framingham study) the distribution of angina pectoris could be different from cases which consult physicians This hypothesis is very unlikely especially in view of the very divergent proportions On the other hand, one may question the validity of history taking In fact, in the above mentioned study from Framingham for the purpose of explaining the striking frequency of the remission rate of angina pectoris the authors discussed the possibility of faulty interpretation of the angina symptom complex For the rejection of this possibility they argued that the veracity of the clinical conclusion could not be judged against laboratory evidence (including coronary arteriography) because angina pectoris is by definition the evaluation of the symptomato[illegible] only And although this argument is sound it does not preclude us from questioning the best manner of acquiring and evaluating the historical information Proudfit and associates commented upon the faulty first impression about the diagno-

itral valve prolapse syndrome

o the Editor:

In the March 1979 issue of AMERICAN HEART JOURNAL here appeared several interesting articles about the mitral alve prolapse syndrome. In the study by Udoshi and associates (97:303, 1979) the authors made some interesting bservations regarding time relations between systolic murmur and echocardiographic mitral prolapse. Although the tudy was not primarily designed to evaluate the acoustic haracteristics of the mitral valve prolapse syndrome, I should ike to make some comments regarding these characteristics.

In typical cases the murmur associated with mitral valve rolapse is meso- to telesystolic and there is correlation with he timing of prolapse on echocardiography. On the other and, there are cases of mitral valve prolapse where we can register only early systolic murmurs, but now they do not correspond with the timing of prolapse determined by echocardiography. Of six patients with protosystolic murmur described in the article by Udoshi and colleagues, five had late systolic prolapse and one had holosystolic prolapse.

In those patients with early systolic murmur and late systolic prolapse there need not be any causal relationship between the mitral valve prolapse and the murmur. The latter may represent coincidental murmur of different genesis, for instance an innocent murmur. In such cases the mitral valve prolapse in reality is silent. Perhaps the mitral valve prolapse syndrome only rarely or never causes early systolic murmurs.

There are some practical implications of this presumption. Subjects with systolic murmur which *is related* to the mitral valve prolapse generally have a less favorable prognosis regarding progression of mitral regurgitation or the risk of developing infective endocarditis, when we compare them with those patients who have only an isolated systolic click. Hence in subjects with the mitral valve prolapse syndrome and protosystolic murmur with or without an associated systolic click, the mere existence of the murmur perhaps does not influence the prognosis.

Dr. Zarko Mavrić
Institute for Health Protection
Cardiovascular Department
B. Kidrica 52a, 51000 Rijeka
Yugoslavia

Spontaneous resumption of sinus rhythm after prolonged AF

To the Editor:

In the Case Report of spontaneous resumption of sinus rhythm in an elderly patient after 13 years of permanent atrial fibrillation, Dr. Chevalier (AM HEART J 98:361, 1979) describes a case showing an interesting and a rare event. We had a similar experience with two patients (R I Med J 325, 297 June 1977) who, on recent follow-up visits, have been noted to maintain normal sinus rhythm. As noted also by Dr. Chevalier, we believe that Holzmann's theory offers the best explanation for this phenomenon. We postulated the following. Atrial fibrillation is usually explained on the basis of two mechanisms—i.e., the unifocal theory and the reentry phenomenon (or the circus movement). It is possible that progressive fibrotic changes taking place in the atria may abolish atrial fibrillation. In the case of unifocal theory, the triggering focus may be eradicated as it gets incorporated into the fibrotic process. In the case of the reentry phenomenon, it is possible that the fibrotic process interrupts the reentry pathway and terminates atrial fibrillation. In any case, it is necessary that the sinus node be capable of taking over once atrial fibrillation ceases. If this was not the case, sinus arrest would result on cessation of atrial fibrillation, as was seen in the case described by Reeve and colleagues (AM HEART J 90:127, 1975). Thus the change from chronic atrial fibrillation to spontaneous sinus rhythm probably represents worsening of the conduction system.

Abdul Hakim Khan, M.D.
Brown University
Division of Cardiology
The Memorial Hospital
Pawtucket, RI 02860

Adsorption of NTG

To the Editor:

We agree with Cacace and associates that adsorption of nitroglycerin to glass containers does not create many problems; our own results concerning this item are consistent with their findings. However, the clinical importance is doubtful when you don't know how much NTG is retained in the infusion system. Therefore we conducted an infusion set adsorption study.

NTG solutions were prepared from an ethanolic stock solution containing 1% w/w of NTG by diluting with distilled water to a concentration of 5 mg/ml. The solution was filtered through an 0.2 micron filter and after discarding the first 50 ml. (we found up to 25% decrease of NTG after filtering the first portion) was filled into 5 ml. glass ampules. After sealing, the ampules were heated for 30 minutes at 105 (Branje and Berghuis[1])

Five milliliters NTG was added to 500 ml. of normal saline in a glass bottle and a polyvinyl chloride (pvc) infusion system was connected. Flow rate was kept constant with an Ivac 531 flow controller. Flow rates used were 0.25, 0.50, 0.75, and 1.00 ml./minute (equivalent to 12.5, 25, 37.5 and 50 micrograms per minute, respectively). Samples were retained at zero, 30, 60, 90, 120, 180, 240, 300, and 360 minutes and were immediately assayed by means of the kinetic method of Yap and coworkers. At the same time, samples drawn from the glass container were assayed; this concentration did not change during the experiment.

The results are summarized in Table I. The loss of NTG turns out to be flow-dependent; after a rapid decrease a gradual increase is subsequently seen which perhaps results in a plateau after six hours. For the fastest flow rate this seems to be at 90% of the original concentration, whereas it is only 60% for the lowest.

Most reports concerning the use of NTG infusions don't mention the type of infusion set they use. Our results indicate that this omission is not justified. Much time is spent on determining stability of intravenous fluids in bottles or bags,

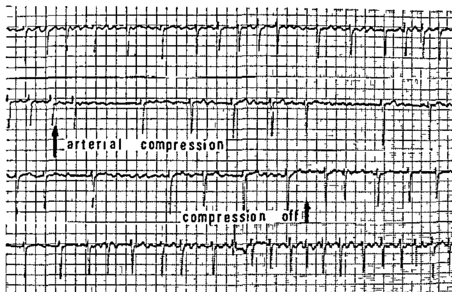


Fig 1 Continuous rhythm strip of a 45 year old woman with multiple A V fistulae in the left thigh. Upon compression of the left femoral artery the ventricular rate slows markedly from approximately 125 beats per minute to approximately 60 beats per minute with resumption of the previous rapid rate when the compression is released

additional example illustrating the great degree to which the atrioventricular node is under the control of the autonomic nervous system

Mayer M Bassan M.D
Department of Internal Medicine
Hadassah Hebrew University
Medical Center
Mt Scopus
Jerusalem Israel

REFERENCES

1 Branham H H Aneurismal varix of the femoral artery and vein following a gunshot wound Internat J Surg 3 250 1890
2 Guyton A C Circulatory Physiology Cardiac Output and Its Regulation Philadelphia 1963 W B Saunders Company pp 366 370

Possible association of pneumonitis with amiodarone therapy

To the Editor

Amiodarone hydrochloride (Cordarone) is an effective agent in the treatment of various arrhythmias We would like to give a brief report on a patient with pneumonitis possibly related to the administration of this drug

A 50 year old male who had suffered myocardial infarction and ventricular tachyarrhythmias received amiodarone 400 mg per day One month later he started to complain of fatigue tachypnea at rest and dyspnea on exertion On examination there were decreased breath sounds but no wheezing or rales The chest roentgenogram showed diffuse interstitial and intra alveolar shadows which were indistinguishable from pulmonary venous congestion (Fig 1) Despite diuretic and digitalis therapy his condition deteriorate matically Pulmonary function tests demonstrated a r tive defect (FVC = 1 95 liters 46% of predicted value severe impairment of gas transfer (pO = 46 mm. pCO = 36 mm Hg) Hemodynamic studies excluded c failure (CI = 3 0 L/min/M PCWP = 2 mm Hg) demonstrated increased pulmonary arteriolar resistanc dyne sec/cm) and increased pressure in the pulm artery (46/16 mm Hg) and right ventricle (46/0 mm H the absence of another apparent cause an adverse react amiodarone was suspected and the drug was disconti Prednisone 60 mg/day was started and the patient's c tion improved rapidly The chest roentgenogram sh complete resolution of the infiltrates (Fig 1) and the pu nary function tests returned to normal

Several factors indicate that the pulmonary manifest and clinical symptoms seen in this patient may be attri to amiodarone First there was a normal base line of pu nary functions before the administration of this drug se there was a latent period between the initiation of therap the onset of illness third amiodarone was the only drug taken by the patient Cessation of this agent and s therapy resulted in a prompt normalization of the cl picture radiologic changes and functional abnormalities chest roentgenogram and pulmonary function tests are patible with hypersensitivity pneumonitis

Heschi H Rotmensch
Meir Liron
Marcel Tupilski
Shlomo Laniado
Municipal Governmental Medical C
Department of Internal Medicine E Hadassah Ho
Pulmonology Unit Ichilov Ho
Department of Cardiology Ichilov Hos
Sackler School of Medicine University of Tel
Tel Aviv I

able I

Parameter	Men (N = 108)		Women (N = 92)	
	Angina pectoris (N = 41)	Non anginal chest pain (N = 67)	Angina pectoris (N = 3)	Non-anginal chest pain (N = 89)
Age (mean ± SD)	59.44 ± 9.25	55.18 ± 9.62	58.50 ± 7.00	54.31 ± 9.71
SBP (mean ± SD)	132.19 ± 37.6	130.97 ± 17.45	15[illegible]0 ± 12.60	137.13 ± 30.50
DBP (mean ± SD)	82.19 ± 21.5	83.50 ± 8.44	83.75 ± 4.78	83.75 ± 15.40
resting HR ($\overline{X}$ ± SD)	69.73 ± 11.87	72.69 ± 12.67	69.00 ± 13.44	71.82 ± 11.95
CTR (mean ± SD)	0.467 ± 0.05	0.457 ± 0.05	0.520 ± 0.07	0.508 ± 0.05
Resting ST T changes (%)	63.4	28.3	66.6	58.4

= standard deviation DBP = diastolic blood pressure SBP = systolic blood pressure HR = heart rate CTR = cardiothoracic ratio.

of angina pectoris, and Welch and co-workers underlined the frequent non-concordance between the history of angina pectoris in women and their findings on the coronarogram.

The superiority of the HIP questionnaire[4] used by us compared to the more conventional one used in the Framingham study lies in the fact that it accounts for not only the positive indicators to the angina symptom complex but also for its negative indicators thus permitting a more balanced evaluation of the chest complaint in a given person. The fact that in women uncomplicated angina pectoris is much more infrequent than in men and even in these women the history of angina pectoris is an insecure predictor of coronary artery disease is corroborated also by elegant correlations with coronarographic and anatomical findings.

In conclusion in reality not only do men far outnumber women for uncomplicated angina pectoris but also the diagnosis of typical angina pectoris in a woman complaining of chest pain is, in the light of our findings very questionable from the beginning and only a very meticulous systematic search and with cross matching history taking can secure a valid conclusion.

Nicholas M. Papa oglou M.D.
Associate Professor University of Athens
Chief of Cardiology Department
5 Hartos Street
Athens 139 Greece

REFERENCES

1. Kannel W B and Sorlie P D. Remission of angina pectoris. The Framingham Study. Am. J. Cardiol 42:119, 1978.
2. Frank C W, Weinblatt E and Shapiro S. Angina pectoris in men: prognostic significance of selected medical factors. Circulation 47:509, 1973.
3. Segal B L. The natural history of angina pectoris *in* Atherosclerosis and Coronary Heart Disease edited by Likoff W., Segal, B L. and Insull, W. New York 1972 Grune & Stratton Inc. pp 231-237.
4. Burch, G E. A Primer of Cardiology 4th edition Philadelphia 1971 Lea & Febiger p 190.
5. Friedberg C K. Diseases of the Heart 3rd edition Philadelphia 1966 W.B Saunders p 718.
6. Proudfit W L, Shirey E K and Sones, F M Jr. Selective cinecoronary arteriography correlation with clinical findings in 1000 patients. Circulation 33:901, 1966.
7. Welch C C., Proudfit W L., and Sheldon W C. Coronary arteriographic findings in 1000 women under age 50. Am J Cardiol. 35:211, 1975.
8. Cohn P F., Gorlin R., Vokonas, P S Williams, R. A., and Herman M V. A quantitative clinical index for the diagnosis of symptomatic coronary artery disease. N Engl. J Med. 286:901, 1972.
9. Detry J M R Kapita B M Cosyns, J., Sottiaux B Brasseur L. A., and Rousseau M F. Diagnostic value of history and maximal exercise electrocardiography in men and women suspected of coronary heart disease. Circulation 56:756, 1977.
10. Diamond G A and Forrester J S. Analysis of probability as an aid in the clinical diagnosis of coronary artery disease. N Engl. J Med 300:1350, 1979.

Branham's sign with atrial fibrillation

To the Editor

In 1890 Branham described the transient slowing of the heart rate which occurs during manual compression of an arteriovenous fistula. We recently encountered a patient who demonstrated Branham's sign in the presence of atrial fibrillation. In surveying the literature and the many hundreds of patients described therein with arteriovenous fistula we were unable to find a case of Branham's sign during atrial fibrillation. Our patient was a 45-year-old female with multiple arteriovenous communications in her left thigh, who had developed congestive heart failure as a result. She had a rapid irregular heart rate of 170 to 130 per minute. Upon manual compression of the femoral artery there was a dramatic and almost instantaneous slowing of the heart rate to approximately 60 beats per minute with an immediate resumption of the rapid rate as soon as the compression was terminated (see Fig. 1).

The mechanism of the phenomenon in atrial fibrillation is undoubtedly the same as in patients with sinus rhythm, namely a reflex response due principally to the increase in blood pressure and the decrease in venous filling. The difference lies in the fact that whereas the exquisite control of heart rate by the automatic nervous system is usually exercised via effects upon the *sinoatrial* node in the patient with atrial fibrillation control is via the *atrioventricular* node. Branham's sign in the presence of atrial fibrillation provides an

Book reviews

Cardiovascular Review By Gerald C Timmis M D Baltimore 1979 The Williams & Wilkins Company 227 pages Price $10 9ɔ

This is a review of the highlights of reports that appeared in American cardiovascular journals for the past 7 years This brief review of selected papers include such a pects of heart diseases as ischemic heart disease valvular heart disease arrhythmias conduction defects effects of therapy and drugs acromegaly amyloidosis asymmetric septal hypertrophy athletic heart cardiomyopathy and others The review is remarkably thorough and extensive for a book of only 227 pages The review like annual reviews in other fields, is useful to many readers but unlike the annual reviews this one includes selected publications over the past 7 years Each statement is well documented to facilitate a more extensive consideration of aspects of cardiovascular problems that might interest the reader As with most reviews of this type this review presents the conclusions and recommendations of the authors of publications without critical analysis of the respective studies

Venous Thromboembolism Prevention and Treatment Edited by John L Madden M D and Michael Hume M D New York 1976 Appleton Century Crofts Inc 240 pages

This small succinct book of 240 pages is concerned with an important problem involving all branches of medicine All physicians are constantly concerned about thromboembolism in all seriously ill patients The many contributors have reviewed the problems effectively and briefly for all physicians The chapters include discussions of risk factors prevention early detection of venous thrombosis pulmonary embolism hemodynamic phenomena diagnosis use of the pneumatic venous pump and prophylaxis Each chapter is appended with a good selection of references The illustrations are good This is a good and useful single source on an important clinical state The papers were presented at a symposium in 1976 in New York City

Hypertension Determinants Complications & Intervention Edited by Gaddo Onesti and Christian R Klimt New York 1979 Grune & Stratton Inc 462 pages Price $39 50

This is the Fifth Hahnemann International Symposium on Hypertension an important and common illness of man The many presentations are grouped into five parts namely determinants complications end organ damage benefit and risk of intervention and therapeutic and preventive trials and community programs It is impossible in a brief review to consider each of the many presentations adequately In general the presentations are good and the discussions up to date The book should interest internists and general practitioners The book fails to date clearly the time of the symposium The great number of publications and symposia on hypertension in recent years makes it unavoidable to repeat what has been said many times and therefore each adds little new to the field Let us hope the next symposium will be limited to only what is new since this fifth one

The Treatment of Acute Myocardial Ischemia An Integrated Medical/Surgical Approach Edited by Lawrence H Cohn M.D., Mount Kιʌo N Y 19˜9 Futura Publishing Company 230 pages Price $23 00

This book by a urgeon of the Peter Bent Brigham Hospital along with contributors from the same hospital representing cardiology in medicine and pathology describes their prac employed in the management of ischemic heart di particularly acute myocardial infarction The book is brief lucid with the emphasis being on integration of the med and surgical specialties The eight chapters include the pat ogy of myocardial infarction pathophysiology surgical t nique and policies for emergency revascularization man ment of unstable angina acute infarction arrhythmias, mechanical complications The principles and pract described seem to be similar to those of other large clir groups found elsewhere in America This book, there outlines very well the practices at the Brigham

Histopathology of Cardiac Arrhythmias By Dr L R Milan 1978 Casa Editrice Ambrosiana 299 pages

This is the second edition on histopathology of car arrhythmias an important publication in cardiology The a tendency to fail to relate the structural changes in myocardium and conduction tissues to function when me ing patients with heart disea_e This book reveals very wel structural changes associated with heart disease Unfo nately the functional state is not necessarily relate explained only by anatomic changes Nevertheless, this l does indicate the pos.ible relationships of structure to f tion both in health and disease The author a patholog t performed an excellent service to cardiology in his studi this publication Rossi has clearly discussed and illustr extremely well the histology of the normal conduction t and morphologic alterations associated with cardiac di along with disturbances in the heart beat The photom graphs are very good and well selected This book shoul studied by all cardiologists It is highly recommended eve pathologists and anatomists

Heart Failure Edited by Alfred P Fishman New York 1 McGraw Hill Book Company Inc 356 pa es

This book contains the presentation on congestive h failure held in honor of Dr Isaac Starr of the Universit Pennsylvania There were many contributors from m parts of the U S A The presentations were concerned basic aspects of myocardial contraction direct assessmen cardiac contraction indirect assessment of cardiac perf ance consequences of heart failure and therapy of h failure Each presentation reflects the opinions and cons ations of the authors The papers are brief and the illu tions and text clearly presented As is true to a great exter present the accuracy of the measurements are not critic discussed and instrumentation is prominent in the prese tions Because recordings are obtained their usefulness is convincing in the understanding of CHF The literature is completely represented A reader who is interested in opinions of the various contributors to the symposium find them clearly expressed in their respective reports.

This reviewer would like to take this opportunity to exp his admiration for Dr Isaac Starr a fine man known for meticulous research and dedication to medicine and who ship Dr Fishman and the steering committee ha e don worthy and admirable job in planning and conducting th symposium With best wishes to Dr Starr an outstandi clinical investigator

Circulatory System Dynamics Edited by Abraham Noordergraaf New York San Francisco and London 19 8 Academ Press, Inc. 3ɔ1 pages Price $36 00



Fig 1 Posteroanterior x ray views of a 50-year old male patient *Left panel* Film taken on August 6 1978 (patient receiving amiodarone) shows diffuse interstitial and intra alveolar shadows. *Right panel* Film taken on August 16 19/8 after stopping amiodarone and with prednisone shows complete resolution of the infiltrates.

REFERENCES

1 Rosenbaum M B Chiale P A Halpern M S Nau G J., Przybylski, J Levi, R J Lazzari J O and Elizari, M V Clinical efficacy of amiodarone as an antiarrhythmic agent, Am J Cardiol. 38 934 1976
2 Holoye P Y., Luna M A MacKay B and Bedrossian C W M Bleomycin hypersensitivity pneumonitis, Ann Intern Med 88 47 1978
3 Carlson J E., and Villavences J W Hypersensitivity pneumonitis due to pyrethrum Report of a case J.A.M.A 237 1718 1977

Announcements

II World Congress of Cardiac Rehabilitation

The second World Congress on Cardiac Rehabilitation will be held on November 30 through December 3 1981 in Jerusalem Israel. For further information contact Secretariat II World Congress on Cardiac Rehabilitation POB 16271 Tel Aviv Israel.

ISFC International Lecture

Dr Edgar Haber Dept of Cardiology Massachusetts General Hospital, Boston will be the first International Lecturer of the International Society & Federation of Cardiology His lecture entitled "Immunological probes in cardiovascular disease will be given at the Royal College of Physicians, London at 6 00 P M on December 4 1980 under the chairmanship of Sir Douglas Black President, Royal College of Physicians. Dr Haber will also deliver ISFC lectures in Edinburgh and Glasgow (details to be published later) All lectures are sponsored by May & Baker Ltd., Dagenham Essex, England For further information, contact Madame Marianne de Figueiredo Central Office International Society & Federation of Cardiology P O Box 117 CH 1211 Geneva 12 Switzerland. Telephone (022) 476755

IX World Congress of Cardiology

The IX World Congress of Cardiology will be held in Moscow U.S S R on June 20 through 26, 1982. Further information is available from Secretariat Organizing Committee USSR Cardiology Research Center Petroverigski per 10 Moscow 101837 U.S S R

International Symposium on Urokinase

The second International Symposium on Urokinase will be held in Geneva Switzerland, on April 27 and 28, 1981. Under the auspices of an international scientific committee, the scientific program will include lectures on these topics basic studies on urokinase urokinase in ophthalmology controlled trials in deep vein thrombosis new aspects of urokinase therapy in pulmonary embolism and other aspects of urokinase therapy Deadline for receipt of abstracts is February 2[illegible] 1981 For further information, contact Professor P M Mannucci, Via Pace 15 20122 Milan Italy

This is a very good review of the important procedures employed in medicine and physiology which relates the role of bioengineering to the study of normal and abnormal circulatory function The author included reviews of the circulatory system blood flow measurements arteries veins, microcirculation and the heart Anyone seriously involved in cardiology should find the book extremely interesting. The author does not exhaust the subjects selected for his ten chapters nor does he include a careful review of the literature but the presentations selected are important ones briefly reviewed as he considers the engineering and biophysical applications to understanding the behavior of the circulation Even though this book is not written for practicing cardiologists those in training in cardiology should know these selected principles of hydrodynamics and hemodynamics This is a good small book (first volume on biophysics and bioengineering) by Noordegraaf who has devoted much time to bioengineering

Critical Cardiac Care Volume V Edited by Ephriam Donoso M D and Stafford I Cohen M D New York 1979 Stratton Intercontinental Medical Book Corporation 248 pages Price $?8 50

The volume of *Current Cardiovascular Topics on Critical Cardiac Care* contains 13 chapters on important acute problems in cardiology Among the subjects discussed are acute myocardial infarction arrhythmias cardiogenic shock acute left ventricular congestive heart failure hypertensive crises surgical emergencies and nursing care This is a practical clinical publication which presents the current concepts and practices in diagnosis and management Readers will find this book to really consist of a series of 13 separate papers each reflecting the contributors points of view Students, interns residents and fellows in medicine and cardiology as well as general practitioners and internists would find the volume to be helpful Surely differences of opinion will become evident as each paper is studied This is a good clinical book for the practicing doctor The reader should realize that the views expressed in this publication reflect to a great extent mainly those of the authors

Cardiology Update Reviews for Physicians By Elliot Rapaport Editor in Chief New York 1979 Elsevier Publishing Company 364 pages Price $?4.95

Cardiology Update is another annual review of cardiology This volume is well written and authentic Some of the subjects included are echocardiography cardiac blood pool imaging and myocardial imaging pulmonary nuclear scanning hemodynamic studies cardiac pacing role of coronary bypass surgery aortic counterpulsation and management of hypertension The many discussions are clearly presented There is no doubt that it is much more effective to study the original publications. However this book is a concise source of discussions of important aspects of cardiology This is a good book for the busy physician

Books received

Fundamentals of Mobile Coronary Care second edition By Leonard B Rose M D and Beatrice K Rose M D Baltimore 1979 The Williams & Wilkins Company 116 pages Price $13 00

Artificial Cardiac Pacing Edited by Edward K Chung M D F A C P F A C C Baltimore 1978 The Williams & Wilkins Company 391 pages Price $34 00

Respiratory Physiology—the Essentials second edition By John B West M D Ph D Baltimore 1979 The Williams & Wilkins Company 182 pages Price $11 50

The Handbook of Critical Care Medicine Edited by Max Harry Weil, M D Ph D., and Robert J Henning M D., New York 1979 Fischer Medical Publications 205 pages.

Cardiac Valve Prostheses By Edward A Lefrak and Albert Starr New York 1979 Appleton Century Crofts Inc 419 pages Price $?4 50

The Biochemistry of Atherosclerosis Edited by Angelo M Scanu with Robert W Wissler and Godfrey S Getz Associate Editors New York 1979 Marcel Dekker Inc., 548 pages. Price $49 75

now commercially available) so as to produce two rates of infusion a basal rate of 50 μL/hr and an eightfold higher rate for mealtimes The high rate is activated by the patient pressing a guarded button on the side of the pump the rate automatically returning to the basal after a pre set period currently 17 minutes The pump receives 2 or 3 ml disposable plastic syringes filled with highly purified porcine insulin (Actrapid Novo Industri Copenhagen) diluted as necessary for each patient with 0 154 mol /L saline according to insulin requirements (see below)

The pump weighs about 300 g measures about 7 by 14 by 2 cm and is worn by the patient on a belt around the waist or in a special shoulder harness

Insulin is delivered from the infuser via a fine nylon cannula (Portex Ltd) which is implanted in the subcutaneous tissue of the anterior abdominal wall [1] This area was chosen to minimize the effects on insulin absorption known to occur when insulin is injected subcutaneously into exercising limbs Extra fine cannulae were used to avoid discharge of insulin from the tip due to random flexing and in the hope of these cannulae being more biocompatible

A single cannula has been used at the same site for 2 months without problems normally they are changed every 2 to 3 weeks Infection has not been observed at the implantation site and no tissue reaction has been felt or observed Other workers have employed a fine metal needle attached to connecting tubing for administration and this needle is changed daily by the patient

Infusion strategy

Control on the patient s conventional regime is used as the basis for setting the initial insulin infusion rate The same total daily dose is generally infused on day 1 (including mealtime step ups) and subsequently the dose is increased or decreased in approximately 20% steps according to the blood glucose levels achieved The basal infusion rate was about 1 3 to 1 8 U /hr in most of our patients other workers have quoted 12 5 to 15 mU /kg /hr the mealtime increase is activated 30 minutes before breakfast lunch and the evening meal

In a study of six patients undergoing CSII at home for prolonged periods (2 to 4 months) subjects were taught to monitor their own blood glucose with glucose oxidase reagent strips (Dextrostix) either estimating the value from the color chart provided or reading the value in a reflectance meter [11] When blood glucose readings exceeded 10 mmol /L they were instructed to initiate an extra high rate infusion When values exceeded 15 mmol /L they injected soluble insulin (Actrapid) by conventional means at a separate subcutaneous site and telephoned for advice—in case there was system malfunction or intercurrent infection for example Syringes were replaced by the patient daily

Blood glucose control

We have considered that the aim of this technique is to keep blood glucose concentrations below about 10 to 11 mmol /L (180 to 200 mg /100 ml) since there is epidemiological evidence from the Bedford and Whitehall population surveys in England[1] and from studies in the Pima Indians of Arizona[11] that significant microvascular complications do not develop in patients with post load blood glucose values below this level [1]

In (fully ambulant) diabetic subjects treated by CSII on a metabolic ward for up to 4 days mean daily blood glucose levels ranged from 5 5 to 8 4 mmol /L After initial adjustments in dose hypoglycemia did not occur as confirmed by significant reduction in the M value (an arbitrary measure of control which increases with both hyper and hypoglycemia and has extra weighting for low values')

Patients who were treated at home for 2 to 3 months (maximum 111 days) had estimated mean ± S D blood glucose levels over the entire period of between 4 8 ± 1 6 and 7 5 ± 1 6 mmol / L [1] Glycosylated hemoglobin assay confirmed that glycemic control was brought into the normal or borderline diabetic range

Intermediary metabolite control

We tend to think of diabetes as a condition characterized sine qua non by abnormalities of glucose metabolism Of course there are many other intermediary metabolites which are disordered in diabetes' and might equally or alone be responsible for the tissue complications By the same score hormones such as glucagon' and growth hormone are present in increased amounts or at least inappropriately high amounts for the level of glycemia The concept of control is obviously becoming much wider particularly as our understanding of the cause of diabetic microangiopathy is so deficient

American Heart Journal

October 1980 Volume 100 Number 4

Editorials

A new approach to improved metabolic control in diabetics: Continuous subcutaneous insulin infusion

J. C. Pickup, M.A., B.M., B.Ch., D.Phil.
London, England

In recent years great efforts have been placed in developing new methods of improving control in insulin dependent diabetic patients. The main incentive is the increasing realization that the late tissue complications of diabetes, particularly the microangiopathies, almost certainly depend for their evolution on the duration and severity of the metabolic disorder of diabetes.[1] If these abnormalities of metabolism could be returned towards normal, it may then be possible to slow, halt, or reverse the progress of retinopathy, nephropathy, and neuropathy in diabetic subjects.

Unfortunately, this postulate of a link between control and complications is still an article of faith rather than a reality and the major stumbling block is the difficulty or (some would say) impossibility of achieving and maintaining metabolic near normality using conventional insulin injection therapy. Clearly what is required is a prospective controlled trial between patients randomly allocated their prevalent insulin therapy ("ordinary control") or a "super control" regime. It is to achieve the strict control of the latter type that various mechanical devices are currently being investigated.

At the outset we know that these devices must fulfil certain criteria. They should be free from complications at the point of insulin delivery to the body; one would expect prolonged intravenous administration to be unsuitable because of the risks of thrombosis and infection. They must not restrict the physical activity of the patient; bulky bedside apparatus like the so called artificial pancreas is thus excluded. Furthermore, such devices must be of low cost and applicable to most types of diabetic patients so as to enable random allocation to a fairly large trial group of patients.

Our approach has been continuous subcutaneous insulin infusion (CSII) using a dual rate portable syringe pump.[2] As will emerge, most or all of the above requirements are met by this system. The absence of a large subcutaneous pool of depot insulin, the rapid mobilization of the small volumes delivered, and the inherent flexibility of the apparatus in which the diabetic patient has control over the rate of insulin delivery commended it as a potential method of achieving long term strict control which was acceptable to the patient.

Technique

CSII is an "open loop" device, i.e., it does not employ continuous blood glucose sensing with feedback control on insulin delivery as does the artificial pancreas,[3] and for this reason alone it becomes smaller, less complex, more reliable, and truly portable. Our prototype delivery system was a modification of a quartz crystal controlled single rate syringe pump, the Mill Hill Infuser

From the Unit for Metabolic Medicine, Guy's Hospital Medical School, London, England.

Received for publication Sept. 6, 1979.

Reprint requests: Dr. J. C. Pickup, Unit for Metabolic Medicine, Guy's Hospital Medical School, London SE1 9RT, England.

0002-8703/80/100417 + 04$00.40/0 © 1980 The C. V. Mosby Co.

insulin withdrawal if the delivery cannula is accidently removed from the subcutaneum or during intercurrent stress and illness blood glucose values can rise quickly and ketosis may develop Prompt corrective action in these circumstances must be taken on the basis of frequently monitored blood glucose estimations Until a reliable metabolic sensor is developed which will warn of loss of control outpatient use of open loop systems should probably remain a research procedure under the closest supervision

Trends

Further miniaturization of infusers will make them more acceptable to larger numbers of diabetic patients The sophistication of micropro cessor control may in the future add great flexibility of infusion rates and offer monitoring facilities and say audible warning of pump malfunction

The dream of an implantable insulin delivery system is still far from being realized New meth ods and routes of administration of insulin need to be evaluated CSII is but one approach Perhaps the greatest priority is for a controlled prospective and randomly assigned trial testing the effects of prevalent and super control on microangiopathy Only then will we be certain of the therapeutic intensity to be used toward achieving good control even with conventional treatments

REFERENCES

1 Cahill, G F Etzweiler D D., and Freinkel, N Blood glucose control and diabetes Diabetes 25 237 1976
2 Tchobroutsky G Relation of diabetic control to devel opment of microvascular complications Diabetologia 15 143 1978
3 Albisser A M and Leibel, B S The artificial pancreas Clin Endocrinol Metab 6 457 1977
4 Pickup J C Keen, H., Parsons J A. and Alberti K G M M Continuous subcutaneous insulin infusion an approach to achieving normoglycaemia Br Med J 1 204 1978
5 Pickup J C Keen, H Parsons J A. and Alberti, K G M M Continuous ubcutaneous insulin infusion good blood glucose control for up to 4 days Diabetologia 16 385 1979
6 Pickup J C Keen H Parsons, J A Alberti, K G M M. and Rowe A S Continuous ubcutaneous insulin infusion improved blood glucose and intermediary metabolite control in diabetics Lancet 1 1255 1979
7 Parsons J A Rothwell, D and Sharpe J E A miniature syringe pump for continuous administration of drugs and hormones the Mill Hill Infuser Lancet 1 77 1977
8 Koivisto V A and Felig P Effects of leg exercise on insulin absorption in diabetic patients, N Engl J Med 298 79 1978
9 Tamborlane W V Sherwin R S Genel, M and Felig, P Reduction to normal of plasma glucose in juvenil diabetes by subcutaneous administrations of insulin with a portable infusion pump N Engl. J Med. 300 573 1979
10 Tamborlane W V., Sherwin, R S Genel, M. and Felig P Restoration of normal lipid and amino acid metabolism in diabetic patients with a portable insulin infusion pump Lancet 1 1258 1979
11 Pickup J C Keen H., Stevenson R W Parsons, J A. Alberti K G M M., White M and Kohner E. M. Insulin via continuous subcutaneous infusion, Lancet 2 988 1978
12 Pickup J C White M C Keen H Kohner E. M. Parsons, J A and Alberti, K G M. M Long term continuous subcutaneous insulin infusion in diabetics at home Lancet 2 870 1979
13 Jarrett R J., and Keen, H Hyperglycaemia and diabetes mellitus Lancet 2 1009 1976
14 Rushforth, N B Miller M and Bennett P H Fasting and two hour post load glucose levels for the diagnosis of diabetes The relationship between glucose levels and complications of diabetes in the Pima Indians, Diabetologia 16 373 1979
15 Keen H., Jarrett R J and Alberti, K G M. M. Diabetes mellitus a new look at diagnostic criteria Diabetologia 16 283 1979
16 Schlichtkrull, J., Munck O., and Jersild M The M value an index of blood sugar control in diabetics. Acta Med Scand. 177 95 1965
17 Service F J., Molnar G D Rosevear J W Ackerman. E., Gatewood, L. C and Taylor W F Mean amplitude of glycemic excursions a measure of diabetic instability Diabetes 19 644 1970
18 Alberti, K G M M Dornhorst A and Rowe A S Metabolic rhythms in normal and diabetic man Studies in insulin treated diabetes Isr J Med. Sci. 11 51 1975
19 Unger R H and Orci, L. Role of glucagon in diabetes. Arch Intern. Med 137 48 1977
20 Lundbaek K Christensen N J Jensen V A., Johansen K Steen Olsen T Prange Hansen A Ørskov H and Østerby R Diabetes diabetic angiopathy and growth hormone Lancet 2 131 1970
21 Pickup J C Home P and Keen, H Unpublished data
22 Champion M Shepherd G Rodger H. W and Dupré J Continuous ubcutaneous insulin infusion in treat ment of diabetes mellitus (Abstract) Diabetes 28 381
23 Stevenson R W Personal communication
24 Katsalambros, M., Verykokidou H Philipides, P Moiras G K., and Daikos G K Comparison of intravenous and subcutaneous insulin infusion in man, Lancet 1 609 1979
25 Dandona P Foster M., Healey S Greenbury E., and Beckett, A G Low dose insulin infusion in diabetic patients with high insulin requirements Lancet 2 283 1978
26 Keen H., and Chlouverakis C An immunoassay method for urinary albumin at low concentrations. Lancet 2 913
27 Viberti, G C Pickup J C., Jarrett R. J and Keen H Effect of control of blood glucose on urinary excretion of albumin and β microglobulin in insulin-dependent diabetes N Engl J Med 300 638 1979
28. Tattersall, R. B Brittle diabetes, Clin Endocrinol. Metab 6 403 1977

It was encouraging that in our initial studies of patients treated by CSII for just 24 hours not only blood glucose but also blood lactate and pyruvate the ketone body 3 hydroxybutyrate and the major gluconeogenic precursor alanine were also returned towards nondiabetic concentrations[8] Tamborlane and associates[4] have found that plasma cholesterol triglyceride free fatty acids and branched chain amino acids are also restored to normal after 7 to 14 days of CSII

There is no information yet on whether glucagon growth hormone and other counter regulatory hormones are normalized during subcutaneous infusion

Insulin levels and doses

Fasting plasma free insulin concentrations during CSII are about 10 mU /L ' i e not far removed from those of the nondiabetic subjects Pharmacokinetic studies are beginning to indicate that the peak of circulating insulin following the mealtime step up is at about 75 minutes so that activating the prandial rate 30 minutes before a meal and allowing 45 minutes for peak glucose absorption should produce a best fit of insulin and nutrients '

It is interesting to note that work in animals indicates that about 50% of the insulin injected subcutaneously is destroyed (presumably digested by proteolytic enzymes) and so it never reaches the blood in biologically active form This probably also applies to humans One may speculate that the small volumes infused would suffer less enzymatic destruction and lead thereby to improved control

Control and microvascular disease the kidney

Radioimmunoassay of urinary albumin has demonstrated that elevated albumin excretion rates are present in some diabetic subjects even before the onset of clinical proteinuria—i e that detectable by reagent strips such as Albustix This microalbuminuria seems to be mainly caused by increased glomerular capillary permeability rather than by renal tubular dysfunction It is not known whether microalbuminuria progresses to clinical diabetic nephropathy but it must at least be taken as an index of small vessel abnormalities in diabetes

CSII has recently been used to establish 1 to 3 days of near normoglycemia in a group of seven insulin requiring diabetic subjects of long known duration of diabetes who were known to have increased urinary albumin excretion during conventional therapy Even over this short period of good control microalbuminuria was reduced in all patients and was normalized in three

These patients must presumably have structural changes in the glomerular capillaries—e g basement membrane thickening So fast was the change in permeability as to suggest functional rather than structural alterations during metabolic near normalization It follows that even in some long standing diabetic patients glomerular permeability can still be returned to normal and perhaps then nephropathy can be delayed More work is needed in this area

Control and microvascular disease the eyes

Two patients treated for 3 months by CSII had at the start of therapy rapidly progressing florid diabetic retinopathy Serial fluorescein angiograms were used to assess the response to near normoglycemia In one patient (mean ± S D blood glucose 5 9 ± 2 0 mmol /L) the progress of the retinopathy was halted and in the other case (mean ± S D blood glucose 6 1 ± 2 1 mmol /L) the retinopathy markedly regressed

Interpretations must of course be guarded in a condition known to suffer spontaneous variations in clinical course However there seems good reason to believe that even severe retinal microangiopathy may respond to super control

Cautions

One type of diabetic subject who may be unsuitable for CSII is the truly brittle patient We should be careful to define this condition as a rare syndrome of wide fast and unpredictable swings in blood glucose seemingly unrelated to food exercise or insulin administration Control does not seem to be much improved in the few brittle patients we have studied Perhaps mechanisms such as variations in subcutaneous absorption and endogenous insulin production are unchanged by this approach at least when using the present simple infusion strategy

As in all open loop systems patients treated by CSII have little or no insulin reserve The subcutaneous pool during infusion is small one factor which may explain why hypoglycemia is not a big problem compared with intensified efforts at good control using conventional depot therapy However it does mean that during absolute or relative

many significant differences from voluntary continuing smokers This investigation established empirically that a voluntary ex smoker is on the average a different kind of person from the persistent smoker and has a lower risk of CHD regardless of smoking[6] Even if no such difference had been demonstrated the drawing of conclusions about causality from comparisons between voluntary ex smokers and voluntary continuing smokers would remain illegitimate An epidemiology that sanctioned such conclusions would have no claim to be scientific

How then can we establish cause? Several attempts have been made to circumvent the difficulties that arise from the heterogeneity within human populations and the phenomenon of self selection The rigorously controlled intervention study referred to above has been approached by Rose and Hamilton Male smokers were allocated randomly (a) to the intervention group which was subjected to intensive advice to give up smoking or (b) to the normal care group which received no special advice over and above that encountered in ordinary life The "intensive advice was successful in reducing average levels of smoking in the intervention group much more than those in the normal care group However up to 1978 the death rate in the intervention group was 1 74 per 100 man years (based on 98 deaths) the rate in the normal care group was slightly but not significantly lower at 1 63 per 100 man years based on 94 deaths Findings for specific causes of death were not reported but because in the general male population of comparable age deaths from diseases of the circulatory system constitute nearly 50% of the total it seems unlikely that mortality from this cause was reduced appreciably in the intervention group These data therefore do not bolster the causal hypothesis

Twin pairs discordant for smoking habits have great research potentiality but as the Surgeon General notes 'The result has been inconclusive The main practical difficulty for this kind of investigation is of course the limitation imposed by small numbers particularly of monozygotic (MZ) twins who tend to be highly concordant for smoking habits In the largest survey published so far Cederlof and associates recorded only seven deaths from CHD in the pooled low group of smoking discordant MZ twins and nine in the pooled high group of present smoker co twins The corresponding findings fo[r] smoking discordant pairs of dizygotic (DZ) tw[in] pairs were 12 deaths (pooled low") and 26 death[s] (pooled high) This latter ratio is in line wi[th] the value expected on both causal and constitu[tional] tional views Among smoking discordant MZ tw[in] pairs the simplest constitutional hypothe[sis] would predict equal numbers of deaths in th[e] low and high smoking groups whereas pure causal theory would predict equality [of] ratios in series of similarly discordant MZ and D[Z] pairs Neither the causal nor the constitutiona[l] theory is excluded by these small numbers Th[e] trend favors constitutional and combined (caus[al] plus constitutional) interpretations

Unfortunately studies of twins remain subje[ct] to certain ambiguities even when numbers a[re] large[9] If for example deaths in smoking M[Z] twins were found to exceed those in their no[n] smoking co twins we would be unable to disti[n]guish between the *causal* hypothesis "smoki[ng] causes CHD and the *converse causal* hypothe[sis] CHD or an associated condition causes t[he] habit of smoking Equal numbers of deaths [in] the two groups would favor neither of these h[y]potheses and would point to a constitution[al] interpretation

One type of evidence that *in principle* cou[ld] distinguish between causal and converse caus[al] hypotheses on the one hand and constitution[al] hypotheses on the other is that which relates [to] secular (temporal) change On a causal hypoth[e]sis a change in cigarette consumption should [be] followed by a change in mortality rate the ma[g]nitude and sign of which should be consiste[nt] with the strength of the causal connectio[n] According to the converse causal hypothes[is] changes in CHD or an associated condition cau[se] the changes in smoking If that hypothesis hold[s] then changes in CHD mortality rate might eith[er] precede or follow corresponding changes in smo[k]ing If neither the causal nor the converse caus[al] hypothesis is valid then no systematic correl[a]tion between the trends in cigarette consumptio[n] and CHD mortality rate should be observed.

In practice secular trends abound in complic[a]tions not the least of which is the inaccuracy [of] death certification coupled with changes in th[e] International Classification of Diseases secul[ar] changes in other causal factors have also to b[e] considered By good fortune neither complicatio[n] appears to be as serious in connection with CH[D]

Smoking and coronary disease

P R J Burch PhD
Leeds England

According to Feinstein[1] a "licensed epidemiologist" can obtain and manipulate the data in diverse ways that are sanctioned not by the delineated standards of science but by the traditional practice of epidemiologists. In this absence of delineated standards it is scarcely surprising that different investigators draw diametrically opposed conclusions. Thus we find on the one hand Shimkin proclaiming "If there is any summit of achievement in cancer research during the past several decades it must be the discovery, irrefutable proof and obvious importance of the fact that tobacco smoking causes lung cancer in man and is associated with other severe hazards to health." By contrast Oldham concludes "we still do not know how cigarettes cause lung cancer nor even if we are particularly rigorous in our use of scientific logic whether they do."

A similar confusion prevails in connection with ischemic heart disease. Perhaps the most detailed exposition of the thesis "cigarette smoking is a cause of coronary heart disease" is given in the recent report by the Surgeon General. Remarkably, the thesis rests on only two types of epidemiological evidence neither of which nor both jointly are adequate to establish cause.

Inevitably the first type of evidence concerns the positive graded association that has generally but not invariably been observed between smoking and the risk of death from ischemic heart disease. Needless to say the Surgeon General is well aware that association does not necessarily imply causation: the link could be explained if people who were constitutionally liable to heart attacks were also constitutionally liable to smoke. (I should add that a positive association is neither a sufficient nor even a *necessary* condition for causation. As pointed out previously in this JOURNAL, a negative genetic association between the predisposition to smoke and the predisposition to a disease could mask a weaker causal connection.)

The Surgeon General dismisses the constitutional alternative by invoking the second type of epidemiological evidence. It should be noted however that the fact that risk in smokers reverts to normal or nonsmokers' levels after they cease to smoke is contrary to the constitutional concept. Curiously, the fact itself is denied by the entries in the Surgeon General's own Table 5—the risk of death from coronary heart disease (CHD) in each of the eight categories of persons who had discontinued smoking for five or more years lies between the levels in comparable "current smokers" and "never smokers."

However, the claim that this evidence is contrary to the constitutional concept is fallacious. If from a population of smokers certain individuals were selected *randomly* by the investigator and were successfully persuaded to give up smoking and if in all other pertinent respects they did not differ on the average from those randomly selected smokers not subjected to such persuasion and who continued to smoke then a significant reduction of mortality in the ex smoker group relative to that in controls would render the constitutional hypothesis improbable to an extent determined by the level of statistical significance. But a comparison of mortality rates in voluntary *self selected* ex smokers with that in voluntary self selected continuing smokers cannot discriminate between causal and constitutional hypotheses. A recent study of voluntary ex smokers *before* they stopped smoking showed

From the Department of Medical Physics, University of Leeds, Leeds, England.

Received for publication Oct. 10, 1979.

Reprint requests: Prof. P. R. J. Burch, Dept. of Medical Physics, University of Leeds, The General Infirmary, Leeds LS1 3EX, England.

0002-8703/80/100421 + 03$00.30/0 © 1980 The C. V. Mosby Co.

Clinicopathological study of the heart and coronary arteries of autopsied cases from the community of Hisayama during a 10-year period Part IV QS waves in the precordial leads

Yuichi Hiyoshi M D *
Teruo Omae M D
Yasuo Hirota M D **
Moriyuki Takeshita M D ***
Kazuo Ueda M D
Masahiro Nakano M D
Seiji Tanaka M D
Hisao Ikeda M D
Shibanosuke Katsuki M D ****
Fukuoka Japan

Myocardial infarctions unrecognized during life were frequently found at autopsy In the epidemiological study of coronary heart disease the scalar electrocardiogram is employed as one of the most useful tools in the diagnosis of this disease and frequently offers unequivocal objective evidence of its presence However it is well known that abnormal Q and QS waves in the precordial leads are seen also in persons without myocardial infarction Some of these waves are transient

From the Second Department of Internal Medicine Faculty of Medicin Kyushu Uni ersity Fukuoka Japan

Supported n part by United State Publ c Health Service (rant No NB-03642 from the National In titute of Neurological Diseases and Bl ndness

Received for publication Dec 26 1979

Accepted for publication March 3 1980

Reprint requests Teruo Omae M D Second Department of Internal Medicine Faculty of Medicine Kyushu University Maidashi 3-1 1 Higashiku Fukuoka 812 Jap n

*Present address First Dept of Internal Medicine School of Medic ne Fukuoka University Fukuoka J pan

**Present address D pt f Internal Med cin Kyushu Dent l College Kitakyushu J p n

***Present addres Ky h Rosa Hospital Kitakyushu Japan

****Present addres Med l College of M yazaki Miyaz ki J pan

Surawicz and colleagues[1] suspected that 0 5% of the electrocardiograms examined had an absent R wave in Lead V_3 Jedlicka reported that QS and QR forms were observed in Lead V_1 in 2 or 3% However the frequency of QS waves in the precordial leads without infarction is not known in the general population

This report concerns QS waves in the precordial leads found in persons of an autopsy series from a Japanese community Hisayama town during a ten year period and further shows the limitations of the scalar electrocardiogram in the diagnosis of myocardial infarction especially a old one

Materials and methods

Hisayama town is a farming community adjoining Fukuoka City on Kyushu island Japan[3] The population in this community was 6 521 in 1960 7 140 in 1965 and 7 154 in 1970 by national census Population distribution by a e and sex was not substantially different from the rest of Japan[3] The residents aged 40 years or over have participated in periodic medical examinations offered by us since the year 1961[4] Participation rates of the residents in the biennial examinations were approximately 90% except for one

0002 8703/80/100424 + 09$00 90/0 © 1980 The C V Mosby Co

as might be expected[6] Analysis implies that the rate of smoking associates inversely with the duration of the average *latent period* between the initiation of the disease process and death from CHD[5] High levels of smoking associate with a short latent period and relatively early death while nonsmokers enjoy a long latent period and a relatively long life If smoking *causes* CHD by (plausibly) shortening the latent period then because the average daily rate of smoking is much higher in young and midde aged men and women than in old persons then the latent period normally constant with age in other diseases should increase with rising age where CHD is concerned Furthermore over the period 1921 to around 1962 7 when cigarette consumption in both sexes in England and Wales was rising the latent period should have shortened the reduction should have occurred earlier in men than in women

None of these expectations of the causal theory is borne out by the mortality statistics[5] The average latent period appears to be almost constant throughout the adult range it was also nearly constant (tending to increase if anything in middle aged women) from 1921 to 1973 Nevertheless large increases in the levels of fatal CHD were recorded but these were unaccompanied by a systematic shortening of the latent period The simplest interpretation of the increases is that they were the consequence at least in part of earlier under recognition of the disease the extent of under diagnosis appears to have been fairly uniform in both sexes up to about the age of 75 A constant factor of under diagnosis would not distort estimates of the duration of the latent period

We have to consider the possibility that changes in other risk factors might have occurred so as to oppose and cancel those caused by the changes in smoking habits This is not impossible although bearing in mind the large differences in the secular changes of smoking by the two sexes and their marked age dependence the demands made of the hypothetical counter acting factors are formidable Changes in diet especially the consumption of animal fats and cholesterol cannot be invoked because on a causal hypothesis they would have exacerbated the effects of smoking over a substantial part of the period 1921 to 1973[10]

To the best of my knowledge the three kinds of investigation discussed here—random intervention trials studies of smoking discordant twins and secular trends—provide the only epidemiologically based evidence that bears critically on the causal versus the constitutional alternative The evidence available so far does not allow us to conclude that smoking causes ischemic heart disease

REFERENCES

1 Feinstein A R Methodologic problems and standards in case control research, J Chronic Dis 32 35 1979
2. Shimkin M B In the middle 1954 63—Historical note J Natl Cancer Inst 62 1295 19 9
3 Oldham P D *Discussion of* Smoking and lung cancer the problem of inferring cause J R Statist Soc A 141 460 1978
4 Surgeon General s Report Smoking and Health, Washington D C 1979 U.S Government Printing Office U S Dept of Health Education and Welfare
5 Burch, P R J Coronary disease Risk factors, age and time AM HEART J 97 415 1979
6 Friedman G D Siegelaub A. B Dales, L. G., and Seltzer C C Characteristics predictive of coronary heart disease in ex smokers before they stopped smoking comparison with persistent smokers and nonsmokers J Chronic Dis 32 175 1979
7 Rose G and Hamilton P J S A randomized controlled trial of the effect on middle aged men of advice to stop moking J Epidemiol. Community Health 32 275 1978
8 Cederlof R Friberg L. and Lundman T The interactions of smoking environment and heredity and their implications for disease etiology Acta Med Scand Suppl. 612 1977
9 Burch P R J Twin studies in relation to the mechanisms of age-dependent disease Acta Med Auxol 8 87 1976
10 Burch, P R J Coronary heart disease risk factors and ageing Gerontology 24 123 1978

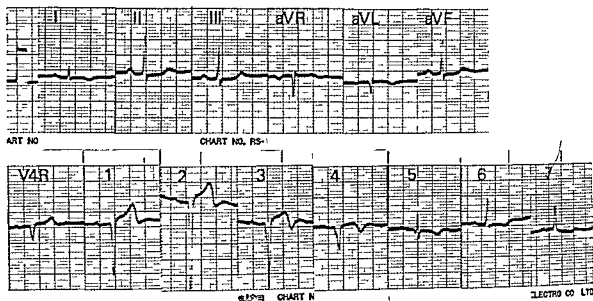


Fig 1 S A 58-year old male tracing made May 30 1963 The patient had a typical cardiac pain in October 1959 and was treated under the diagnosis of myocardial infarction This tracing shows an abnormal Q wave in Lead aV_L and QS waves in Leads V_R through V The T wave was inverted in Leads I aV_L and V and was terminally inverted in Leads V through V Postmortem examination revealed a healed myocardial infarction involving the anteroseptal and lateral walls of the left ventricle

in origin Five of these subjects showed left ventricular hypertrophy pattern by voltage criteria (RV_5 or $RV_6 + SV_1 > 35$) as well Leads in which QS waves were present are summarized in Table III Four persons showed QS waves in Leads V_{4R} and V_1 and one individual exhibited these waves in Leads V_{4R} through V_2 The other eight subjects showed an initial R wave in the leads to the right of those with QS waves A normal initial R wave in the leads farther to the right did not imply that the QS wave was pathognomonic of myocardial infarction Fig 2 reproduces the tracing of one of these individuals

Electrocardiograms of seven subjects showed QS waves in the precordial leads and a left ventricular hypertrophy pattern QS waves were present in Leads V_R and V_1 or in V_{4R} through V_2 in all of these tracings In all of them QS waves were deep and the elevated ST segment showed upward concavity T waves in the right precordial leads were upright in six individuals In the other subject QS waves in the right precordial leads were accompanied by an upright T wave in one year and by an inverted T wave in another year One subject showed clockwise rotation as well

Two individuals showed complete left bundle branch block in other years Therefore QS waves in these persons may be due to incomplete left bundle branch block One of these individuals showed left ventricular hypertrophy pattern The tracings of one case are reproduced in Fig 3

In two subjects dilatation of the right atrium was considered to be responsible for QS waves in the right precordial leads A shallow QS wave with an isoelectric ST segment was present in Lead V_1 in both of these individuals In one of them, P waves in Leads II and III were upright and sharp and a slurred r wave was present in Leads aV_R and V_{4R} Dilatation of the right atrium was recognized at autopsy (Fig 4) In the other subject P waves in Leads II and III were not large but dilatation of the right atrium and ventricle was found at autopsy

Electrocardiograms with precordial QS waves and clockwise rotation were recognized in five subjects QS waves were present in Lead V_R and V_1 in three of them QS waves were found in Leads V_{4R} through V in one year and in Leads V_R through V_3 in another year in one subject In the other individual QS waves were localized in Leads V_{4R} through V_3 in one year and in Leads V_{4R} through V_2 in three other years (Fig 5) QS waves were not deep in four of the five individuals The ST segment was elevated in four of the five subjects T waves were upright in two individuals and were inverted in the other two subjects The other subject showed ST segment elevation with an inverted T wave in one year and an

year At every periodic examination a resting electrocardiogram was taken from each participant with flat hot stylus type machines using the standard 12 leads plus Leads V_{3R} and V_7 The recording speed was 25 mm per second All of the electrocardiograms were read by Dr Hirota at each examination For this study the electrocardiograms of the autopsied persons were reexamined by Drs Hirota and Hiyoshi.

All efforts were made to obtain an autopsy on all of the deceased persons in this community[2] The number of autopsied persons aged 40 years or over at the time of death was 339 (181 men and 158 women) during the first ten year period from Nov 1 1961 to Oct 31 1971 Distribution of these by age and sex is presented in Table I The mean *autopsy rate was approximately 84%*

Heart and coronary arteries were examined after fixation in 10% formalin The subepicardial coronary arteries were cut transversely at 2 to 3 mm intervals and both of the ventricles were also cut transversely at 1 cm intervals from the apex to the base Histological examination was made on one of the transverse sections containing both papillary muscles and also on the section containing suspected lesions A zone of necrosis or scarring of 1 cm or more in the maximal dimension was called myocardial infarction Lesions of histological age of 5 weeks or more using the criteria described by Mallory and colleagues were considered old

Results

Electrocardiograms had been taken from 308 (161 men and 147 women) of the 339 autopsied persons at least once during the periodic examinations QS waves in the precordial leads were recognized in 46 persons (21 men and 25 women) Excluding WPW syndrome and complete bundle branch block none of the features of the electrocardiogram other than QS and abnormal Q waves was considered in the selection of cases Distribution of individuals by the number of tracings displaying precordial QS waves is presented in Table II

There were nine individuals exhibiting old myocardial infarction (anteroseptal six anteroseptal lateral one circumferential two) QS waves were limited to the Lead V_{3R} through V_2 in two V_{4R} through V_3 in four and V_{3R} through V in three In all of them QS waves were accompanied by ST segment elevation excluding Lead V_{3R} QS waves were deep in all subjects Abnormal Q wave in the lead farther to the left was found in only one of these nine individuals In all but this one subject the q wave was not recognized in the left precordial leads In eight subjects the elevated ST segment showed upward concavity In the other one the ST segment showed upward convexity but review of the history revealed no evidence suggestive of acute myocardial infarction at the time of this examination The T wave was upright or terminally inverted in the leads with a QS wave in eight individuals In the other subject the T wave was upright or terminally inverted in Leads V_{3R} through V_2 and was inverted or terminally inverted in Lead V_3 showing the QS wave In four patients precordial QS waves were recorded at the examination in 1961 In two individuals they appeared at the third examination following symptoms suggestive of myocardial infarction In the other three subjects they appeared in the later tracings but symptoms suggestive of myocardial infarction were not revealed by a review of the history Fig 1 is a reproduction of the tracing of one of the infarction cases

In 13 persons without myocardial infarction q waves in Leads V_5 V_6 or V_7 suggested that QS waves in the right precordial leads were positional

Table I Age and sex distribution of autopsied persons by 10 year age groups

Sex	Age groups (years) 40-49	50-59	60-69	70-79	80-89	90-99	Total
Men	13	20	54	64	23	7	181
Women	8	18	28	55	41	8	158
Total	21	38	82	119	64	15	339

Table II Distribution of individuals by number of tracings with QS waves in one or more precordial leads from V_1 to V_6*

Sex	Number of tracings 1	2	3	4	5	6	Total
Men	10	4	2	2	1	1	20
Women	7	11	3	1	0	4	26
Total	17	15	5	3	1	5	46

*Numbers from whom electrocardiograms were taken 308 (161 men and 147 women)

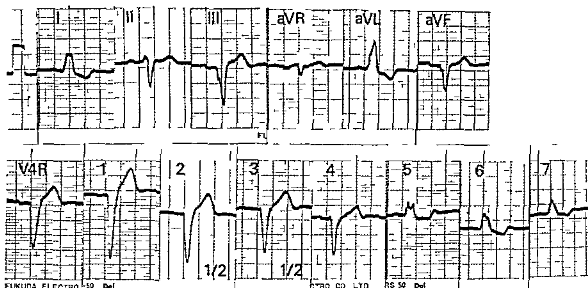


Fig 3A K K. 79 year-old male tracing made May 6 1965 This tracing shows complete left bundle branch block

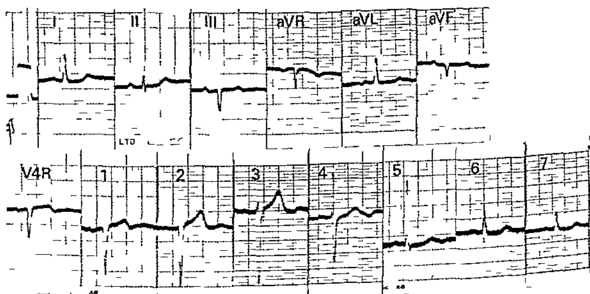


Fig 3B This tracing was taken on May 21 1966 It shows QS waves in Leads V and V QS waves in these leads may be due to incomplete left bundle branch block. The subject died 2 years later of pancreatic cancer Heart weight was 240 gm

cardial infarction case can be normal in some years[1 1]

The most important criterion of the scalar electrocardiogram for the diagnosis of old infarction is the presence of QS and/or abnormal Q waves However cases of QS waves in the precordial leads especially in the right precordial leads without myocardial infarction were frequently reported An abnormal Q or QS wave in the right precordial leads was reported to be recognized in the cases of septal infarction,[16] left ventricular hypertrophy,[1 17 19] right ventricular hypertrophy and dilatation [19 2] right atrial dilatation[19] primary myocardial disease amyloidosis[1 r n] acute ischemia of the myocardium[2 7] left bundle branch block left anterior hemiblock[8] septal focal block clockwise rotation pulmonary emphysema[18 30 31] deformity of the thorax[19] allergic shock[3] acute adrenal failure[18] acute pancreatitis[33] cerebrovascular diseases[31 3 35] elec

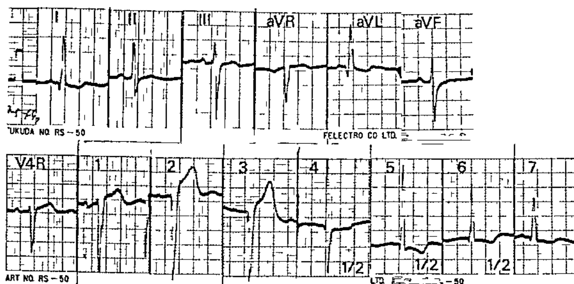


Fig 2 U K 70 year old male tracing made May 14 1962 This tracing shows a left ventricular hypertrophy pattern Lead V shows a QS wave with embryonal r wave Leads V through V show a q wave Postmortem examination revealed left ventricular hypertrophy (heart weight 510 gm)

isoelectric ST segment with an upright T wave in another year

Electrocardiograms of eight individuals showed QS waves in the right precordial leads but they were otherwise within normal limits Localization of precordial QS waves is summarized in Table IV In all of these subjects initial r waves appeared in Lead V or V_3 and increased in amplitude to an R wave in leads farther to the left QS waves of six subjects were small Autopsy revealed slight to severe pulmonary emphysema in five individuals subdural hematoma in one liver cirrhosis in one and acute intoxication with insecticide in one subject In one individual having pulmonary emphysema left ventricular hypertrophy (heart weight 335 gm) was recognized at autopsy

Electrocardiograms with precordial QS waves were tabulated by the localization of a QS wave and the presence or absence of myocardial infarction (Table V) The categories for the localization are not mutually exclusive This table indicates that QS waves localized to only one Lead—V V or V_3—were frequently not due to myocardial infarction All of the electrocardiograms with a QS wave in one Lead (V_2 *or* V_3) or in leads V *and* V_3 had a q wave in the left venticular leads Therefore these QS waves were considered to be positional Even if an initial r wave was present in leads farther to the right these electrocardiograms should not always be interpreted as being due to myocardial infarction solely on the basis of QS waves Electrocardiograms with QS waves in Leads V and V_2 should also be carefully interpreted

QS waves with an embryonal r wave were found in six subjects All of them had an embryonal r wave on the descending limb of the QS wave In two of them myocardial infarction was recognized at autopsy All of the subjects with myocardial infarction had deep QS waves but persons without infarction also frequently showed deep QS waves Development of the precordial QS waves in the second third or later tracing was found in both groups with and without myocardial infarction

Discussion

Electrocardiogram shows age trends [6] sex differences [8] and racial differences Constitutional differences also induce electrocardiographic differences The electrocardiogram is not sensitive to coronary atherosclerosis [6 10 1] Myocardial infarction develops in only a small number of the cases of coronary atherosclerosis

The clinical diagnosis of myocardial infarction without electrocardiographic evidence has been shown to be inaccurate However it is well known that there are difficulties in the diagnosis of myocardial infarction by scalar electrocardiogram Rigid criteria will improve specificity but will reduce sensitivity The tracings of the myo

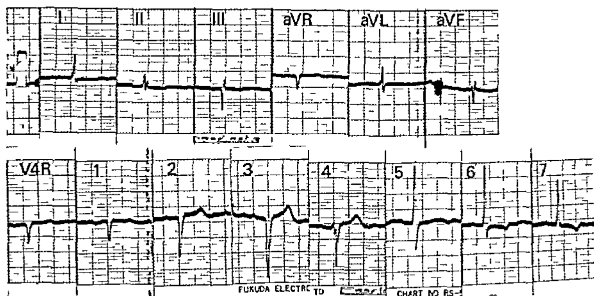


Fig 5 F T 83 year old female tracing made May 21 1962 This tracing shows QS waves in Leads V through V and clockwise rotation The subject died of hemorrhagic brain infarction in December 1962. Heart weight was 280 gm

Table IV Individuals with precordial QS waves without other electrocardiographic abnormalities

Leads with QS wave	*Men*	*Women*	*Total*
V_R and V	2	4	6
V_R through V	0	1	1
V and V in one year and V through V in another year	1	0	1

trophy In clockwise rotation the interventricular septum rotates and the right septal surface faces anteriorly or even slightly toward the left and therefore the septal vector seems to be directed toward the left Myers and co workers[16] maintained that in left ventricular hypertrophy cardiac rotation brought the right atrium beneath the sternum and tilted the mitral orifice to the right and foward and that in such a position left ventricular cavity potential could be recorded in Leads V_1 and V Surawicz and associates[1] were of the opinion that in left ventricular hypertrophy the initial vector forces were directed downward which caused the initial negative deflection of the QRS complex in Leads V_3 andV_4 and that the tracings recorded from the position below the standard level of V_3 and V_4 showed an initial R wave

Epstein and Wasserburger [8] reported a case of pulmonary emphysema where QS waves in Leads V_1 through V_6 were attributed to the low level of

Table V Distribution of individuals by localization of QS wave and by presence or absence of myocardial infarction

Localization of QS wave	*Myocardial infarction*			
	+		−	
	Men	*Women*	*Men*	*Women*
V through V	3	0	0	0
V through V	3	3	1	[illegible]
V and V	1	2	6	5
V and V	0	0	1	1
V	0	0	1	0
V	1	0	4	3
V	0	1	9	15

*The categories for the localization are not mutually exclusive.

the diaphragm In this case tracings taken from the position two intercostal space below the standard level were normal Some of our cases suggested that absence of the initial R wave in the precordial leads resulted from a transitional zone effect Absence of the initial R wave in the right precordial leads can theoretically occur either because of a change of heart position with relation to the electrode or because of a change of the electrode position with relation to the heart[1]

From the foregoing it would appear that the diagnosis of myocardial infarction must never rest solely upon a single tracing The electrocardiographic findings should be evaluated in the light of the clinical findings and the history The

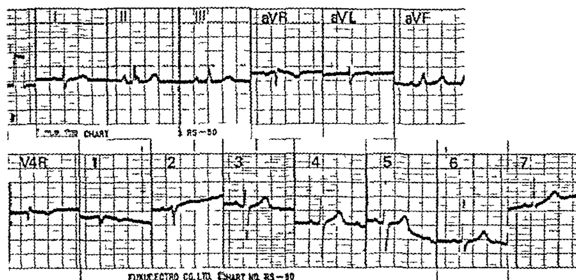


Fig 4 K M 80-year old male tracing made May 28 1963 P waves in Leads II and III were upright and sharp R waves in Leads aV_R and V were small but slurred A QS wave was present in Lead V Autopsy revealed a patent foramen ovale accompanied by dilatation of the right atrium and a dilated and thickened pulmonary artery

trolyte imbalance [1, 6, 36] normal heart WPW syndrome [35] etc

Our cases did not suffer from acute adrenal failure acute pancreatitis acute cerebrovascular diseases asthmatic attack or angina pectoris at the time of examination

Infarction in the left half of the interventricular septum can produce a QS wave in the right precordial leads and disappearance of a q wave in the left ventricular leads These changes are attributed to disappearance of the left to right septal vector The presence of a normal initial r wave in Lead V_{3R} indicates that a QS pattern in Leads V_1 and V is the result of infarction and not a normal variant and the abnormal Q waves demonstrated in leads farther to the left constitute indirect evidence that the QS complexes in Leads V_1 and V are also the results of infarction [16] Myers and associates reported that a smooth QS wave in Leads V and V might occur as a normal variant but that a Q wave followed by a small R wave or R wave equivalent and then by a deep S wave was representative of septal infarction Our cases however suggest that the notched QS wave in the right precordial leads are not pathognomonic of septal infarction The ST segment and T wave are also changed in the acute stage of infarction The level of the S T junction and the contour of the ST segment is of little or no aid after healing [1]

Transitory appearances of the QS wave or

Table III Localization of QS waves in the precordial leads

Leads with QS wave	*Men*	*Women*	*Total*
V and V	1	3	4
V through V	0	1	1
V	1	0	1
V	1	1	2
V or V from year to year	1	0	1
V through V V through V_{3R} V and V or V_{3R} from year to year	0	1	1
V_{3R} or V and V_{3R} from year to year	1	0	1
V and V or V_{3R} from year to year	1	0	1
V and V or V from year to year	0	1	1

abnormal Q wave in tachycardia [5] angina pectoris or acute pancreatitis were considered due to acute ischemia of the myocardium DePasquale and colleagues [6] reported that local electrolyte disturbance could cause abnormal Q and QS waves Haiat and Chiche reported that a transient abnormal Q wave appeared more frequently in the precordial leads than in Leads II III and aV_F In left anterior hemiblock the initial vector is directed inferiorly and a Q or QS wave is recorded in the right precordial leads In left bundle branch block the initial R wave may be absent in the right precordial leads because the normal depolarization of the septum is disturbed Incomplete left bundle branch block is frequently associated with left ventricular hyper

problems in electrocardiography Ann Intern Med 52 587 1960
21 Chou T C Pseudo infarction (Noninfarction Q waves) Cardiovasc Clin 5(3) 199 1973
22 Pec L and Enderle J Ondes Q pathologiques en l absence d infarctus du myocarde Classification et considérations électrophysiologiques Acta Cardiol 24 242 1969
23 Buja L M Khoi N B and Roberts W C Clinically significant cardiac amyloidosis Clinicopathologic findings in 15 patients Am J Cardiol 26 394 1970
24 Roesler H and Dressler W Transient electrocardiographic changes identical with those of acute myocardial infarction accompanying attacks of angina pectoris Am Heart J 47 520 1954
25 Rubin I L Gross H and Arbeit S R Transitory abnormal Q waves during bouts of tachycardia Am J Cardiol 11 659 1963
26 DePasquale N P Burch G E and Phillips J H Electrocardiographic alterations associated with electrically silent areas of myocardium Am Heart J 68 697 1964
27 Rubin I L Gross H and Vigliano E M Transient abnormal Q waves during coronary insufficiency Am Heart J 71 254 1966
28 Farnham D J and Shah P M Left anterior hemiblock simulating anteroseptal myocardial infarction Am Heart J 92 363 1976
29 Gambetta M and Childers R W Rate dependent right precordial Q waves Septal focal block Am J Cardiol 32 196 1973
30 Zuckermann R Cabrera E Fishleder B L and Sodi Pallares D *Electrocardiogram in chronic cor pulmonare* Am Heart J 35 421 1948
31 Littmann D The electrocardiographic findings in pulmonary emphysema Am J Cardiol 5 339 1960
32 Rosenfeld I Silverblatt M L and Grishman A Allergic shock in humans Report of two cases with electrocardiographic findings Am Heart J 53 463 1957
33 Fulton M C and Marriott H J L Acute pancreatitis simulating myocardial infarction in the electrocardiogram Ann Intern Med 59 730 1963
34 Pfister C W and De Pando B Cerebral hemorrhage simulating acute myocardial infarction Dis Chest 42 206 1962
35 Menon S Electrocardiographic chan es simulating myocardial infarction in cerebrovascular accident Lancet 2 433 1964
36 Nora J R and Pilz C G Pseudoinfarction pattern associated with electrolyte disturbance Arch Intern Med 104 300 1959
37 Myers G B Klein H A Stofer B E and Hiratzka T Normal variations in multiple precordial leads Am Heart J 34 785 1947
38 Ruskin J N Akhtar M Damato A N Ticzon A R Lau S H and Caracta A R Abnormal Q waves in Wolff Parkinson White syndrome Incidence and clinical significance J A M A 235 2727 1976
39 Haiat R and Chiche P Transient abnormal Q waves in the course of ischemic heart disease Chest 65 140 1974
40 Lipman B S Massie E and Kleiger R E Bundle branch block *in* Clinical Scalar Electrocardiography Chicago 1973 Year Book Medical Publishers Inc pp 138-186
41 Blackburn H Classification of the electrocardiogram for population studies Minnesota Code J Electrocardiol 2 305 1969
42 Blackburn H Keys A Simonson E Rautaharju P and Punsar S The electrocardiogram in population studies A classification system Circulation 21 1160 1960
43 McNeil B J Keeler E and Adelstein S J Primer on certain elements of medical decision making N Engl J Med 293 211 1975

IMPORTANT
INFORMATION FOR AUTHORS

All manuscripts for the AMERICAN HEART JOURNAL should be sent to

Dean T Mason M D
Section of Cardiovascular Medicine
University of California
School of Medicine
Davis California 95616

electrocardiogram may also be better interpreted on the basis of pattern reading in the mass population survey for coronary heart disease Persons displaying precordial QS and abnormal Q waves in the standard electrocardiogram should be evaluated by further examination including tracings taken from the lower levels Minnesota Code 1 1 [1] seems to have some difficulties in the diagnosis of myocardial infarction Blackburn and colleagues[6] stated that false positive labels of infarction on the basis of Q and QS criteria would be reduced in the final tabulation by excluding subjects with chronic pulmonary disease The false positive diagnosis of myocardial infarction by QS waves in the right precordial leads would be further reduced by excluding persons with q waves in the left precordial leads

As the accuracy of a diagnostic test is influenced by the prevalence of the disease of interest in the population studied [13] the precordial QS waves may have a higher diagnostic value in the population with higher prevalence of coronary heart disease

Summary

During a ten year period from November 1 1961 to October 31 1971 339 residents aged 40 years or over at death were nonselectively autopsied in a Japanese community Hisayama town (mean autopsy rate 84%) One or more standard 12 lead ECGs plus V_R and V electrocardiograms taken at periodic medical examinations were available for 308 of them In 46 persons QS waves were localized in one or more leads from V to V By transverse sectioning of the hearts old myocardial infarction extending into the interventricular septum was found in nine of these 46 persons Frequency of myocardial infarction cases in each category for QS localization was as follows Lead V_1 to V_4 three of three Leads V to V six of nine Leads V and V_2 three of 15 Leads V and V_3 none of two Lead V none of one Lead V_2 one of eight and Lead V one of 25

The authors acknowledge the support of the faculty of the First and Second Departments of Pathology Kyushu University

REFERENCES

1 Surawicz B Van Horne R G Urbach, J R and Bellet S B QS-and QR pattern in leads V and V in absence of myocardial infarction Electrocardiographic and vectorcardiographic study Circulation 12 391 1955

2 Jedlicka J The differential diagnostic significance of the Qr and QS pattern in lead V Cardiologia 52 1 0 1968

3 Hiyoshi Y Omae T., Takeshita M Ueda K., Hirota Y Katsuki S Tanaka K., and Enjoji M Malignant neoplasms found by autopsy in Hisayama Japan during the first ten years of a community study J Natl. Cancer Inst 59 13 1977

4 Hiyoshi, Y Omae T., Takeshita M., Ueda, K., Katsuki S Tanaka K and Enjoji, M Clinicopathological study of the heart and coronary arteries of autopsied cases from the community of Hisayama during a 10 year period—I Ischemic myocardial lesions J Chronic Dis 31 313 1978

5 Mallory G K., White P D., and Salcedo-Salgar J The speed of healing of myocardial infarction A study of the pathologic anatomy in seventy two cases Am Heart J 18 647 1939

6 Blackburn H., Vasquez C L and Keys, A The aging electrocardiogram A common aging process or latent coronary artery disease? Am. J Cardiol 20 618 1967

7 Simonson E The effect of age on the electrocardiogram Am. J Cardiol. 29 64 1972

8 Simonson, E Blackburn H Jr Puchner T C., Eisenberg P., Ribeiro F and Meja M Sex differences in the electrocardiogram Circulation 22 598 1960

9 Marmot M G Syme S L. Kagan A., Cohen J B., and Belsky J Epidemiologic studies of coronary heart disease and stroke in Japanese men living in Japan Hawaii and California Prevalence of coronary and hypertensive heart disease and associated risk factors, Am J Epidemiol. 102 514 1975

10 Benchimol A., Harris, C L., Desser K B., Kwee B T., and Promisloff S D Resting electrocardiogram in major coronary artery disease J.A M.A 224 1489 1973

11 Froelicher V F., Jr., Yanowitz F G., and Thompson A J The correlation of coronary angiography and the electrocardiographic response to maximal treadmill testing in 76 asymptomatic men Circulation 48 597 1973

12 Master A M Dack S and Jaffe H L Cardiac efficiency and prognosis following recovery from acute coronary occlusion. The results of various functional tests J.A M.A 120 1271 1942

13 Kaplan B M and Berkson D M Serial electrocardiograms after myocardial infarction Ann. Intern Med 60 430 1964

14 Anderson N and Skjaeggestad Ø The electrocardiogram in patients with previous myocardial infarction Acta Med Sand 176 123 1964

15 Burns Cox C J Return to normal of the electrocardiogram after myocardial infarction Lancet 1 1194 1967

16 Myers G B., Klein H A and Hiratzka T Correlation of electrocardiographic and pathologic findings in infarction of the interventricular septum and right ventricle Am Heart J 37 720 1949

17 Myers, G B QRS-T patterns in multiple precordial leads that may be mistaken for myocardial infarction I Left ventricular hypertrophy and dilatation Circulation 1 844 1950

18 Epstein M and Wasserburger R H Electrocardiograms simulating myocardial infarction in the presence of normal coronary arteries Review of the literature and presentation of ten illustrative cases Vasc Dis. 4 215 1967

19 Myers, G B QRS-T patterns in multiple precordial leads that may be mistaken for myocardial infarction II Right ventricular hypertrophy and dilatation, Circulation 1 860 1950

20 Burch G E DePasquale N., and Malaret G Selected

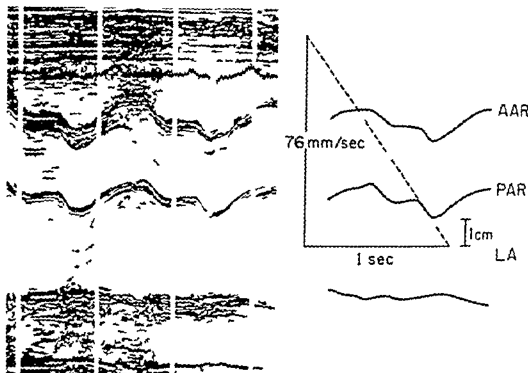


Fig 1 Schematic representation of the method used to calculate the aortic root slope *AAR* = anterior root *PAR* = posterior aortic root *LA* = left atrium

Table I

	HR (bts / min)	PR (msec)	LA/BSA (mm /M)	TAE (mm)	Ao slope (mm / sec)	LV ESD (mm)	LV EDD (mm)	LV thickness IVS (mm)	LV thickness PW (mm)	AML E to F slope (mm / sec)
Group 1 (No = 25)	61 6 ± 1 6	168 5 ± 5 4	18 5 ± 0 5	10 9 ± 0 6	58 0 ± 1 9	30 4 ± 1 0	48 7 ± 0 8	9 5 ± 0 2	9 ? ± 0 2	99 7 ± 6 0
Group 2 (No = 15)	73 6 ± ? 6	156 5 ± 5 9	20 9 ± 0 6	7 5 ± 0 6	50 6 ± 4 6	29 9 ± 3 0	50 5 ± 3 1	15 4 ± 1 1	13 8 ± 0 5	66 6 ± 5 4
P	< 0 001	NS	< 0 01	< 0 001	NS	NS	NS	< 0 001	< 0 001	< 0 001

Abbreviations HR = heart rate PR = PR interval LA = left atrial echo dimension BSA = body surface area TAE = total diastolic excursion of the posterior wall of the aortic root Ao slope = slope of the posterior motion of the aortic root during atrial contraction LV = left ventricular ESD = echocardiographic end systolic dimension EDD = end-diastolic dimension IVS = interventricular septum PW = posterior wall AML = anterior leaflet of the mitral valve

All values are expressed as the mean ± standard error of the mean

the ECG were determined over a minimum of three consecutive beats (average number of beats analyzed was 4 9 per patient) and the mean was obtained (Fig 1) In all patients the aortic slope always appeared constant during atrial emptying Beat to beat variation was small and each individual value in a given patient was within 10% of the mean for that patient The reproducibility of this measurement determined from serial tracings was excellent and intraobserver variation was less than 5% The total posterior aortic root excursion in a cardiac cycle and left atrial size were also measured in standard fashion Other echocardiographic parameters measured included the E to F slope of the anterior mitral valve leaflet diastolic and systolic left ventricular internal dimensions and the thickness of the septal and posterior left ventricular walls All echocardiograms were recorded on Irex machines utilizing an Aerotech 2 25 mHz transducer

Hemodynamic correlates of late diastolic posterior motion of the aortic root

John A. Ambrose, M.D.
Eulogio E. Martinez, M.D.
Jose Meller, M.D.
Richard Gorlin, M.D.
Augusto D. Pichard, M.D.
Michael V. Herman, M.D.
Louis E. Teichholz, M.D.
New York, N.Y.

Aortic root motion on m mode echocardiography is influenced by left atrial volume change. Analysis of this motion reveals that in diastole there is both an early and late diastolic posterior motion separated at slow heart rates by a period of little motion in mid diastole. This early diastolic motion has been quantified by an atrial emptying index which is the fractional change in diastolic motion of the posterior aortic root in the first one third of diastole.[2] This index is abnormal in mitral stenosis and inversely correlated to the degree of stenosis. However, in addition to left atrial emptying across the open mitral valve, atrial volume change during this period should reflect left atrial filling from pulmonary venous flow.[3] Late diastolic posterior motion of the aortic root occurs as a consequence of left atrial contraction. During atrial systole, however, little or no left atrial filling occurs and, ignoring the possibility of pulmonary venous reflux, left atrial volume change should reflect late diastolic events in the left ventricle. In this paper we have examined the hemodynamic determinants of late diastolic posterior motion of the aortic root following the P wave of the ECG in normal individuals and patients with left ventricular hypertrophy in whom altered patterns of left ventricular filling commonly occur.

Materials and methods

Standard m mode echocardiography was performed on 25 individuals (Group 1) including 21 consecutive normal volunteers and four patients with atypical chest pain with normal coronary arteries and left ventricular function, and on 15 patients (Group 2) with left ventricular hypertrophy (IVS or PW > 11 mm.) secondary to aortic stenosis, hypertension, or idiopathic hypertrophic subaortic stenosis. In addition, the echocardiograms of 10 patients (Group 3) with a clinical diagnosis of mitral stenosis who were in normal sinus rhythm were reviewed. Patients were included only if high quality echocardiograms of the aortic root and left ventricle could be obtained. Patients with left ventricular asynergy, significant coronary artery disease, or more than mild aortic or mitral regurgitation were excluded. The aortic root was recorded at 50 mm./sec. in a sweep from the anterior mitral valve leaflet at the level of the aortic valve. The gain was diminished until a single strong echo could be reflected from each side of the aortic root. Echocardiograms of the aortic root were rejected when several echoes were reflected from both sides of the aortic root or if the anterior and posterior aortic roots were not moving parallel in late diastole. The slope and excursion of the late diastolic posterior motion of the posterior aortic root following the P wave on

From the Division of Cardiology, Department of Medicine, The Mount Sinai Medical Center, New York, N.Y.

Received for publication Feb. 12, 1980.
Accepted for publication April 9, 1980.

Reprint requests: John A. Ambrose, M.D., Division of Cardiology, The Mount Sinai Medical Center, One Gustave L. Levy Place, New York, N.Y. 10029.

0002-8703/80/100433 + 08$00.80/0 © 1980 The C. V. Mosby Co.



Fig 3 Representative echocardiogram of the aortic root in a patient from Group 2 *The arrow is pointing to the LV pressure trace* *ECG* = electrocardiogram *AR* = aortic root *LA* = left atrium

ic and hemodynamic data were available the aortic root slope was correlated with various left atrial and left ventricular parameters Echocardiographic and hemodynamic data from the 16 patients studied at the time of catheterization are given in Table II A significant inverse linear correlation was found between the aortic slope and EDCS ($r = -0.74$ $P < 0.01$) as seen in Fig 5 Because of scatter in the data we did not attempt in the individual patient to predict chamber stiffness from the value of the aortic root slope There was no relationship between aortic slope and either left atrial size total aortic excursion pre A wave pressure A wave height the atrial contribution to LV filling (ΔD) end diastolic dimension of the left ventricle LV wall thickness or left ventricular end diastolic pressure

Discussion

The aortic root and left atrium are easily visualized with m mode echocardiography Although excursion of the aortic root has been related to stroke volume Strunk and co workers were the first to demonstrate that movement of the posterior aortic root during early diastole reflects left atrial volume change Presumably this is related to the relative immobility of the left atrial wall except anteriorly where it comes into contact with the ascending aorta Furthermore Strunk and associates devised an atrial emptying index which measured the rate of emptying of the left atrium in early diastole This index is decreased in the presence of mitral stenosis and also in patients with increased pulmonary capillary wedge pressures and no mitral stenosis' The determinants of late diastolic motion of the aortic root have not been previously characterized In sinus rhythm late diastolic posterior motion of the aortic root is directly related to left atrial contraction and in patients with complete heart block it can be shown to follow the P wave of the electrocardiogram occurring anywhere in ventricular diastole ' It also disappears in the presence of atrial fibrillation We found the slope of late diastolic posterior motion correlated best with a modulus of late diastolic chamber stiffness of the left ventricle but not with the atrial contribution to left ventricular filling or the change in left ventricular pressure following atrial contraction A possible explanation for this association is contained in the appendix

During atrial systole the rate of left atrial volume change (ignoring pulmonary venous reflux) equals the rate of left ventricular volume change as there is no left atrial filling during th period Although the aortic root slope represents

Sixteen patients the four with atypical chest pain in Group 1 and 12 patients in Group 2 in whom high quality echocardiograms of the aortic root and left ventricle could be obtained during diagnostic catheterization were further evaluated with invasive studies Informed consent was obtained in each patient prior to study Either before injection of any contrast agent or at least 20 minutes following completion of catheterization when heart rate and left ventricular end diastolic pressure had returned to baseline a No 8 Millar catheter was externally calibrated and inserted via the brachial artery into the left ventricle As the aortic root slope represents a late diastolic event it was compared with pressure and dimension measurements of the left ventricle in late diastole only Simultaneous pressure and echo dimensions of the left ventricle were obtained before the A wave of the left ventricular pressure trace and at the A wave peak if present (12 patients) or at end diastole (four patients) at a paper speed of 100 mm /second Chamber stiffness in late diastole (EDCS) was determined as $\Delta P/\Delta D$ and divided by the average pressure ($\bar{P}$) This assumes an exponential pressure dimension relationship in late diastole ($\Delta P/\Delta D = K\bar{P}$) even though this curve may be slightly altered by viscous forces occurring at the time of atrial systole[5] McLaurin and colleagues and recently our laboratory have validated the use of dimension in place of volume in determining EDCS At least three consecutive beats were averaged and analyzed with the aid of a Graf pen sonic digitizer and PDP 11/70 computer The calculation of stiffness using this methodology has been previously described All aortic root slopes were calculated at the same heart rate and left ventricular pressure as the other echocardiographic and hemodynamic parameters and were analyzed independently of the hemodynamic data

Statistical analyses were performed using the two tailed t test for difference in means Least squares linear regression analyses was performed and r values were calculated All results are expressed as the mean ± standard error of the mean

Results

Basic echocardiographic data from Groups 1 and 2 are contained in Table I Patients in Group 2 were significantly older had larger left atrial sizes faster heart rates thicker interventricular septums and posterior walls and slower E to F slopes of the mitral valve than in Group 1 patients (all with $P < 0.05$) The total aortic root excursion was significantly greater in Group 1 PR intervals were similar between the two groups The individual aortic root slopes for Groups 1 and 2 are seen in Fig 2 The mean slope of Group 1 was slightly greater than Group 2 although this was not statistically significant A representative aortic root echocardiogram from a patient in Group 2 with a slow aortic root slope is shown in Fig 3 In both groups there was no correlation between either age or heart rate and aortic root slope Patients with mitral stenosis (Group 3) had significantly slower aortic root slopes (28 8 ± 4 5 mm /sec) than in Group 1 or Group 2 ($P < 0.001$) Left atrial sizes in Group 3 (29 ± 1 3 mm /M²) were significantly greater than left atrial sizes in Group 1 or Group 2 ($P < 0.01$) A representative echo of a patient with mitral stenosis is seen in Fig 4 As catheterization data were not available for most of the patients with mitral stenosis no attempt was made to correlate the aortic slope with the degree of stenosis

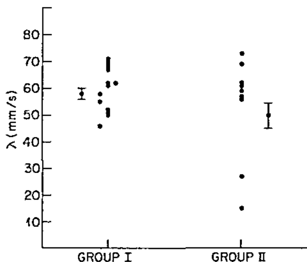


Fig 2 Illustration showing the individual aortic root slopes (λ) for all patients in Groups 1 and 2 The mean ± SEM for both groups is also shown There wa no statistically significant difference between the mean aortic root slopes in the two groups.

Although the mean slope in Groups 1 and 2 were similar a wide range of values was present in Group 2 (15 to 73 mm /sec) Therefore in the 16 patients in whom simultaneous echocardiograph

Table II

No	Age	Sex	HR (bts/min)	PR (msec)	LA/BSA (mm./M)	TAE (mm)	Ao slope (mm/sec)	ESD (mm.)	EDD (mm)	LV thickness		E to F Slope (mm./sec.)
										LVS (mm.)	PW (mm)	
Group II												
1	46	M	80	160	18	10	62	31	50	14	15	70
2	42	M	55	166	21	10	61	33	55	21	16	41
3	50	M	76	144	19	9	40	35	58	13	14	[illegible]
4	65	F	79	153	21	7	56	21	47	13	13	59
5	31	M	68	138	20	12	66	31	55	12	11	108
6	58	F	83	175	24	6	57	30	47	19	14	77
7	50	M	58	120	22	9	43	16	42	12	11	51
8	58	F	83	200	23	5	23	27	48	16	16	44
9	46	M	74	172	22	6	69	29	49	25	16	49
10	41	M	68	200	16	6	46	40	53	19	17	86
11	21	M	83	138	19	7	59	24	43	16	1[illegible]	78
12	56	M	61	134	20	9	73	23	4[illegible]	1[illegible]	11	[illegible]
Group I												
13	50	M	57	121	23	10	52	20	46	10	9	120
14	42	F	61	152	16	7	50	25	42	10	9	[illegible]0
15	40	M	62	172	12	10	46	39	56	11	10	165
16	50	F	65	192	18	12	62	24	48	10	10	95

ΔP = "A" wave height in millimeters of mercury which is the numerator of th stiffness equation $\bar{P}$ = denominator of stiffness equation which is the average pressure during d terminat on of stiffness EDCS = late diastolic chamber stiffness which is equal to $\frac{\Delta p \ \Delta D}{\bar{P}}$ where ΔD is the change in the echocardiographic internal dimension.

left atrial dimensions encountered in our patients Therefore as there may be a linear relationship between atrial dimensions and left atrial angiographic volumes in the range of left atrial dimensions measured a change in dimension of the left atrium would be proportional to a change in volume The aortic root slope as a measure of left atrial volume change would then be independent of left atrial size per se and normalization for left atrial size would not be indicated

It is possible that the differences in slopes found in our patients were primarily related to differences in left atrial contractility On the other hand as we found no relationship between the aortic slope and either left atrial size the posterior aortic root excursion or A wave height differences in the force of left atrial contraction seem unlikely to explain all our findings However it is likely that in patients in Group 1 and Group 2 with similar aortic slopes the higher left ventricular pressures in Group 2 imply a more forceful left atrial contraction as a compensatory mechanism for maintaining equal rates of left atrial emptying

Although we ignored pulmonary venous reflux ultrasonic flow transducers implanted in the pulmonary veins of dogs have shown a brief retrograde pulse during left atrial contraction.[1] Utilizing Doppler techniques retrograde flow in the jugular vein has been demonstrated in patients with abnormal right ventricular compliance and large right atrial A waves[1] However even if pulmonary venous reflux is greatest in patients with large A waves in their left ventricular tracings many of these same patients have increased forward flow into the ventricle from a large atrial contribution to filling In these patients pulmonary venous reflux may be of little importance in determining the aortic root slope

In conclusion we have studied the hemodynamic correlates of late diastolic motion of the aortic root The slope of this line is decreased in mitral stenosis and in the absence of mitral stenosis may be related to diastolic properties of the left ventricle This parameter is easily determined and with future work could become a potentially useful noninvasive index of late diastolic events in the left ventricle

Summary

Motion of the posterior aortic root on echocardiography is related to left atrial volume chan e Early diastolic posterior motion of the aortic root

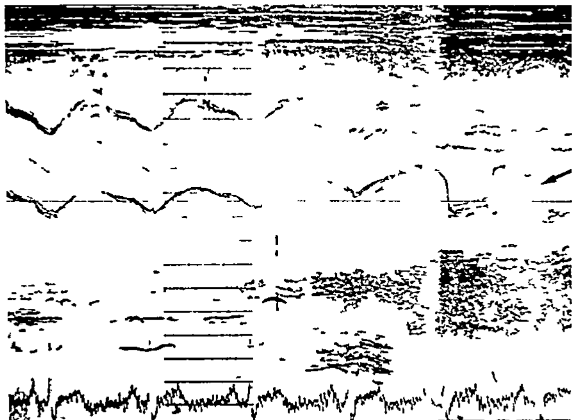


Fig 4 Representative echocardiogram of the aortic root and anterior mitral valve leaflet *(arrow)* from a patient in Group 3

a rate of left atrial dimension change (ΔD/ΔT LA) and not a volume change it seems apparent that this slope should be governed by the filling characteristics of the left ventricular chamber In turn left ventricular diastolic filling is dependent on the chamber stiffness over that portion of the pressure volume or pressure dimension curve measured It would be most informative to have varied left ventricular pressure by changing load ing conditions while measuring chamber stiffness and the aortic root slope to see if a change in slope might accurately predict a change in late diastolic chamber stiffness

There was a good relationship between stiffness and the aortic root slope in the series of patients studied However because of scatter in the data we did not attempt to predict stiffness in the individual patient This suggests that the aortic root slope might also be dependent on other variables not measured—e g left atrial size left atrial contractility and pulmonary venous reflux In this study we did not normalize the aortic root slope for left atrial size since the relationship between left atrial dimension and left atrial vol

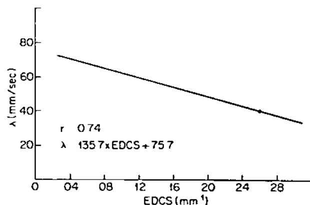


Fig 5 Graph showing the correlation between the aortic root slope (λ) from the 16 patients studied invasively versus end-diastolic chamber stiffness *(EDCS)*

ume has not been clearly defined In children Yabek and co workers [1] found that left atrial echo dimensions and left atrial volumes were related by the equation y = 8 1 x [1] Although this equation is exponential on review of their data from Table I it could also be fit by a straight line with an r value of 0 89 over the same range of

Appendix

1 During atrial systole

$$\frac{\Delta V}{\Delta T}(LA) = \frac{\Delta V}{\Delta T}(LV)$$

If there is no left atrial filling during atrial systole and ignoring pulmonary venous reflux

2 $$\frac{\Delta D}{\Delta T}(LA) \propto \frac{\Delta V}{\Delta T}(LA)$$

If there is a linear relation between atrial dimension and volume[11]

3 $$\frac{\Delta P}{\Delta V}(LV) = K\overline{P} \text{ or } \Delta V = \frac{\Delta P}{K\overline{P}}$$

If an exponential relationship exists between P and V during diastole in the left ventricle

4 Substituting for ΔV in equation 1 the expression $\frac{\Delta P,}{K\overline{P}}$

then $$\frac{\Delta D}{\Delta T}(LA) \propto \frac{\Delta V}{\Delta T}(LA) = \frac{1}{K} \times \frac{\Delta P}{\overline{P}} \times \frac{1}{\Delta T}$$

Therefore $\frac{\Delta D}{\Delta T}$ (LA), which is the aortic root slope is inversely related to

K We found no relationship between the aortic slope and either $\overline{P}$ of ΔP This is probably related to the fact that in this series of patients

$\frac{\Delta P}{\overline{P}}$ remained relatively constant with a wide range of pressure

Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978 Therefore all manuscripts must be accompanied by the following written statement signed by one author The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C V Mosby Company in the event the work is published The undersigned author warrants that the article is original is not under consideration by another journal and has not been previously published I sign for and accept responsibility for releasing this material on behalf of any and all co authors Authors will be consulted when possible regarding republication of their material

Ejection fraction by echo	*Pre "A wave pressure (mm Hg)*	*ΔP (mm Hg)*	*$\bar{P}$ (mm. Hg)*	$\Delta P/\bar{P}$	*EDCS (mm)*
0.67	14.3	16.7	22.7	0.74	0.15
0.69	13.5	8.6	17.8	0.48	0.16
0.69	25.0	22.7	36.4	0.62	0.26
0.86	4.6	2.8	6.0	0.47	0.06
0.73	15.5	7.3	19.2	0.38	0.09
0.66	23.0	14.3	30.2	0.47	0.10
0.91	16.7	11.5	22.5	0.51	0.21
0.51	19.8	11.5	25.6	0.45	0.24
0.70	7.4	6.7	10.8	0.62	0.10
0.49	18.5	13.7	25.4	0.54	0.30
0.74	13.7	6.3	16.9	0.37	0.14
0.81	14.2	7.6	18.0	0.42	0.09
0.87	5.0	8.0	9.0	0.89	0.14
0.42	5.5	5.0	8.0	0.63	0.22
0.56	9.0	6.3	12.2	0.52	0.16
0.61	6.1	6.1	9.2	0.67	0.13

reflects both LA emptying and filling and has been measured as the atrial emptying index To study late diastolic motion of the aortic root we measured the slope of posterior motion of the aortic root after left atrial systole (following the P wave of the ECG) in 25 subjects without heart disease (Group 1) in 15 patients with left ventricular hypertrophy due to pressure overload (Group 2) and in 10 patients (Group 3) with mitral stenosis The aortic root slope measured (mean ± SEM) 58.0 ± 1.9 mm/sec in Group 1 50.6 ± 4.5 mm/sec in Group 2 (NS vs 1) and 28.8 ± 4.5 mm/sec in Group 3 ($p < 0.01$ vs 1 or 2)

In 16 patients (four in Group 1 and 12 in Group 2) studied at catheterization an inverse correlation ($r = -0.74$ $p < 0.01$) was found between the aortic root slope (over a range of 30 to 73 mm/sec) and left ventricular late diastolic chamber stiffness measured with simultaneous left ventricular echo and high fidelity pressure recordings No correlation was found between this slope and either left atrial size total aortic root excursion left ventricular pressure pre A wave height of the A wave end diastolic pressure or the atrial contribution to left ventricular filling Therefore the aortic root slope in late diastole is decreased in mitral stenosis and in the absence of mitral stenosis it appears to be related to late diastolic properties of the left ventricle

We gratefully acknowledge the technical assistance of Mr William B King and Ms Ondilla Bobdilla and the invaluable secretarial assistance of Ms Mercydee Cintron and Mr T Robert Last

REFERENCES

1 Strunk B L Fitzgerald, J W Lipton M Popp R L and Barry W H The posterior aortic wall echocardiogram Its relationship to left atrial volume change Circulation 54 744 1976
2. Strunk, B L London, E J., Fitzgerald J., Popp R L and Barry W H The assessment of mitral stenosis and prosthetic mitral valve obstruction using the posterior aortic wall echocardiogram Circulation 55 885 1977
3 Morgan, B C Abel, F L., Mullins G L and Guntheroth, W G Flow patterns in cavae pulmonary artery pulmonary vein and aorta in intact dogs, Am J Physiol 210 903 1966
4 Akgun G and Layton C Aortic root and left atrial wall motion An echocardiographic study Br Heart J 39 1082 1977
5 Hess, O M., Grimm J and Krayenbuhl H P Diastolic simple elastic and viscoelastic properties of the left ventricle in man Circulation 59 11 8 1979
6 Gaasch, W H Cole J J., Quinones M A and Alexander J K Dynamic determinants of left ventricular pressure volume relations in man Circulation 51 317 1975
7 Kennish, A Yellin E and Frater R W Dynamic stiffness profiles in the left ventricle J Appl Physiol 39 665 1975
8 McLaurin, L P Grossman, W Stefadouros M A Rolett E L and Young D T A new technique for the study of LV pressure-volume relations in man Circulation 48 56 1973
9 Ambrose J A Teichholz L E., Meller J Weintraub W Pichard A D Smith H., Jr Martinez E E and Herman M V The influence of LV late diastolic filling on the A wave of the left ventricular pressure trace Circulation 60 510 1979
10 Wasserman A G Cheng T O and Ross A M The relationship of pulmonary artery wedge pressure to the posterior aortic wall echocardiogram in patients free of obstructive mitral valve disease (Abstr) Am J Cardiol. 43 411 1979
11 Yabek S M Isabel-Jones J., Bhatt D R., Nakazawa M Marks, R A and Jarmakani, J M Echocardiographic determination of left atrial volumes in children with congenital heart diseases Circulation 53 268 1976
12 Sevaciyan V and Ranganathan N Transcutaneous Doppler jugular venous flow velocity recording Circulation 57 930 1978

(For Appendix see next page)

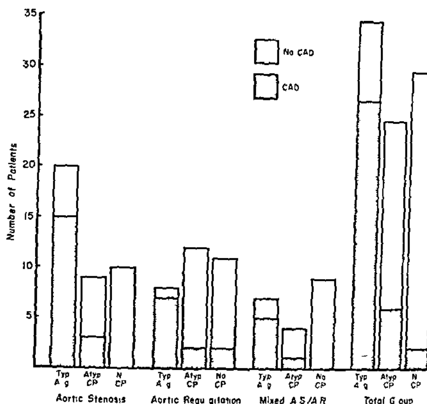


Fig 1 The correlation of angina pectoris and coronary artery disease (CAD) in patients with aortic stenosis (A S) aortic regurgitation (A R) and mixed aortic stenosis and aortic regurgitation (A S/A R) Typ Ang = typical angina pectoris Atyp CP = atypical chest pain No CP = no chest pain

The degree of aortic regurgitation was assessed by root aortography in the left anterior oblique projection[17] Aortic regurgitation was graded as trivial (1+) mild (2+) moderate (3+), and severe (4+) Trivial regurgitation was defined as a mall amount of dye entering the left ventricle during diastole and washing out during systole and severe regurgitation was assumed when good opacification of the left ventricle was seen during the first diastole with the dye remaining in the left ventricle for several beats

The pressures were recorded with a fluid filled manometric system the zero reference point being the mid chest level pressures were recorded on an Electronics for Medicine photographic recorder The aortic valve pressure gradients were measured by recording simultaneous left ventricular and aortic pressures with a double lumen catheter or with two separate catheters The left ventricle was entered retrogradely through the aortic valve or via the transseptal route

Typical angina pectoris was defined as chest discomfort lasting for 1 to 15 minutes precipitated by effort or emotion exposure to cold or at rest which was promptly relieved by rest or nitrates

Atypical chest pain was defined as prolonged chest discomfort lasting sometimes for hours and usually occurring at rest and not relieved by nitrates

The aortic valve area was calculated by means of the Gorlins formula[18]

On the basis of the predominant aortic valve lesion the patients were divided into three sub groups (1) patients with severe aortic stenosis (with a valve area equal to or less than 0 55 cm /M with mild or no associated aortic regurgitation) (2) patients with predominant aortic regurgitation (moderate to severe aortic regurgitation with no pressure gradient or with less than 20 mm Hg peak gradient across the aortic valve) and (3) patients with mixed aortic valve disease (systolic pressure gradient of equal or greater than 20 mm Hg with moderate or severe aortic regurgitation)

Statistical analysis was performed by the chi square method and by the Student s t test

Results

There was a total of 90 patients for our final analysis Sixty patients (66%) had chest pain of

Angina pectoris and coronary artery disease in patients with severe aortic valvular disease

A. Hamid Hakki, M.D.
Demetrios Kimbiris, M.D.
Abdulmassih S. Iskandrian, M.D.
Bernard L. Segal, M.D.
Gary S. Mintz, M.D.
Charles E. Bemis, M.D.
Philadelphia, Pa.

Angina pectoris is a common symptom of both aortic valve disease and coronary artery disease.[1-4] In both conditions the angina is due to an imbalance between oxygen supply and demand. The presence of significant coronary artery disease in patients with aortic valve disease is of predictive value for the operative mortality rate during aortic valve replacement. A recent report indicated that patients with aortic valve disease associated with coronary artery disease undergoing aortic valve replacement and concomitant coronary bypass surgery had better short- and long-term prognoses than did patients who had only aortic valve replacement and no bypass for their coronary artery disease. Therefore, when we consider the possibility of aortic valve surgery it is important to know whether there is associated coronary artery disease. There is, however, a significant controversy in the reported prevalence of angina pectoris or associated coronary artery disease in patients with aortic valve disease.[5, 10-15] The purpose of this study is to review our experience as to the prevalence of angina pectoris and associated coronary artery disease in a group of 90 patients 40 years of age and older with significant aortic valve disease who were studied in our cardiac catheterization laboratory.

Materials and methods

The records of all patients with cardiac catheterization diagnoses of aortic valve disease were reviewed. Only patients over 40 years of age were included in our study. Patients who had more than trivial mitral insufficiency, mitral stenosis, or who had had previous coronary or valve surgery were excluded. Ninety consecutive patients were finally selected for the study. All patients had complete right and left heart catheterization, left ventriculography, aortography, and coronary arteriography. Left ventriculograms were performed in a 30 degree right anterior oblique projection with 45 to 50 ml of 76% meglumine diatrizoate (Renografin). Aortograms were performed in the left anterior oblique projection and coronary arteriography was performed in multiple left and right anterior oblique projections with the Sones and the Judkins technique. Coronary arteriography is routinely performed in our institution in all adult patients with aortic valvular disease.

The cine films were recorded with a 35 mm camera at 30 seconds and were reviewed by at least two angiographers. We calculated the left ventricular volumes using the right anterior oblique projection left ventriculograms.[16] Cardiac output was determined by the dye dilution technique and by the Fick method. The ejection fraction was calculated as angiographic stroke volume divided by the end-diastolic volume. The regurgitant fraction was calculated as the fraction of the total angiographic cardiac output minus the forward cardiac output divided by the total angiographic cardiac output.

From the Likoff Cardiovascular Institute, Hahnemann Medical College and Hospital, Philadelphia.

Received for publication Feb. 14, 1980.
Accepted for publication May 8, 1980.

Reprint requests: Demetrios Kimbiris, M.D., Hahnemann Medical College and Hospital, 230 N. Broad St., Philadelphia, Pa. 1910_.

0002-8703/80/100441 + 09$00.90/0 © 1980 The C. V. Mosby Co.

Table I Clinical hemodynamic, and angiographic data in 90 patients with severe aortic valve disease

	Pts with AS		Pts with AR		Pts with AS AR	
	With CAD (n = 18)	Without CAD (n = 21)	With CAD (n = 11)	Without CAD (n = 20)	With CAD (n = 6)	Without CAD (n = 14)
Age (years)	65 ± 10.1	60 ± 7.8	55.5 ± 7.4	54.5 ± 8.7	67 ± 7.3	57 ± 12.4
Chest pain						
Typical angina	15 (83%)	5 (24%)	7 (64%)	1 (5%)	5 (83%)	2 (14%)
Atypical chest pain	3 (17%)	6 (38%)	2 (18%)	10 (50%)	1 (17%)	3 (22%)
Coronary risk factors						
None	2 (11%)	4 (19%)	2 (18%)	4 (20%)	1 (1 %)	7 (50%)
One or more	16 (89%)	17 (81%)	9 (82%)	16 (80%)	5 (83%)	7 (50%)
Dyspnea on exertion						
NYHA I II	10 (56%)	10 (48%)	3 (27%)	9 (45%)	1 (17%)	3 (21%)
NYHA III IV	4 (22%)	4 (19%)	1 (9%)	6 (30%)	4 (66%)	6 (43%)
Syncope	5 (28%)	8 (38%)	0 0	6 (30%)	0 0	3 (21%)
MI by ECG	2 (11%)	2 (10%)	3 (27%)	0 0	1 (17%)	0 0
Calcified aortic valve	16 (89%)	19 (90%)	4 (36%)	5 (25%)	4 (67%)	10 (71%)
Mean gradient (mm Hg)	57 ± 24	75 ± 23	35 ± 5.3	31 ± 7.4	65 ± 23.8	67 ± [illegible]
AVA cm²/M²	0.35 ± 0.11	0.28 ± 0.07	—	—	—	—
LVEDP (mm Hg)	18.5 ± 10.5	18 ± 8.1	27 ± 13.8	19 ± 10	34 ± 10.3	[illegible] ± 13
CI (L/min/M²)	2.4 ± 0.61	2.4 ± .4	2.5 ± 0.4	2.7 ± 0.6	2.1 ± 0.6	2.4 ± 0.4
LVEF	0.65 ± 0.12	0.63 ± 0.23	0.52 ± 0.06	0.57 ± 0.11	0.5 ± 0.13	0.57 ± 0.19
Coronary artery disease						
1VD	4 (22%)	0	4 (36%)	0	2 (33%)	0
2VD	8 (44%)	0	7 (64%)	0	3 (50%)	0
3VD	3 (17%)	0	0	0	1 (17%)	0
LM	3 (17%)	0	0	0	0	0

Risk factors include history of hypertension diabetes mellitus smoking hyperlipidemia and family history of coronary artery disease

Abbreviations AS = aortic stenosis AR = aortic regurgitation CAD = coronary artery disease AVA = aortic valve area LVEDP = left ventricular end-diastolic pressure CI = cardiac index LVEF = left ventricular ejection fraction ± = one standard deviation 1VD = one vessel disease 2VD = two-vessel disease 3VD = three vessel disease LM = left main coronary artery disease NYHA = New York Heart Association classification (Classes I IV) MI = myocardial infarction ECG = electrocardiogram n = number of patients

2.7 ± 0.6 L/min/M² in the coronary artery disease and non coronary artery disease subgroups respectively The left ventricular ejection fraction was 52 ± 6% and 57 ± 11% for the coronary artery and non coronary artery disease subgroups respectively

Patients with mixed aortic stenosis and aortic regurgitation There were 20 patients in this group 14 men and six women There were six patients (30%) with associated coronary artery disease (mean age 67 ± 7.3 years) and 14 patients (70%) without associated coronary artery disease (mean age 57 ± 12.4 years) Of the six patients with coronary artery disease two had one vessel disease three had two vessel disease and one had three vessel disease (Table I) In the subgroup with associated coronary artery disease all patients had chest pain (five typical angina and one atypical chest pain) Five patients (83%) had one or more risk factors for coronary artery disease and four patients had dyspnea on exertion (New York Heart Association Class III or IV) None of the patients had syncope

There was electrocardiographic evidence of myocardial infarction in one patient In the subgroup without associated coronary artery disease five patients (36%) had chest pain (two typical angina and three atypical chest pain) Seven patients (50%) had one or more risk factors for coronary artery disease Six patients (43%) had dyspnea on exertion (New York Heart Association Class III or IV) three patients (21%) had syncope and none had electrocardiographic evidence of myocardial infarction

On fluoroscopic examination calcification of the aortic valve was seen in 67% and 71% in the subgroups with and without coronary artery disease respectively The hemodynamic data are shown in Table I In the subgroup with coronary artery disease the mean systolic pressure gra

these 35 had angina pectoris (39%) and 25 had atypical chest pain (Fig 1) while only 35 of the 90 patients (39%) had associated coronary artery disease Thirty three of the 35 patients (94%) with coronary artery disease had chest pain (typical angina in 27 and atypical chest pain in six) Two patients with coronary artery disease did not have chest pain One of these patients had 55 to 60% narrowing of the left anterior descending coronary artery the history of the other patient was difficult to obtain because of language difficulty and his chest discomfort could not be evaluated properly Of the remaining 55 patients without coronary artery disease 27 (49%) had chest pain (eight typical angina and 19 atypical chest pain)

The detailed clinical hemodynamic and angiographic data for all groups of patients are summarized in Table I Each of the three groups was further subdivided into two subgroups patients with coronary artery disease and those without

Patients with predominant aortic stenosis There were 39 patients in this group 26 men and 13 women Their ages ranged from 43 to 79 years (mean 65 ± 10 years) Associated significant coronary artery disease was present in 18 patients (46%) one vessel was involved in four patients two vessels were involved in eight patients three vessels were involved in three patients and the left main coronary artery was involved in three patients The remaining 21 patients had no associated coronary artery disease All the 18 patients with associated coronary artery disease had chest pain (typical angina 15 atypical chest pain three) Of the 21 patients without associated coronary artery disease 11 patients (52%) had chest pain (typical angina five atypical chest pain six)

One or more risk factors for coronary artery disease were present in 16 of the 18 patients (89%) with associated coronary artery disease and in 17 of the 21 patients (81%) without coronary artery disease The risk factors were hypertension diabetes mellitus smoking hyperlipidemia and a family history of coronary artery disease under the age of 60 Dyspnea on exertion was present in 14 patients (78%) with coronary artery disease and 14 patients (67%) without coronary artery disease Syncope was present in five (28%) and eight patients (38%) with and without coronary artery disease respectively

Electrocardiographic evidence of myocardial infarction was present in two patients in each subgroup Calcification of the aortic valve was present in 16 patients (89%) with coronary artery disease and 19 patients without The average mean aortic valve pressure gradient was 57 ± 24 mm Hg in the coronary disease subgroup and 75 ± 23 mm Hg for the subgroup without coronary artery disease The average aortic valve area was 0 35 ± 0 11 cm²/M² for the coronary artery disease and 0 28 ± 0 07 cm²/M² for the noncoronary artery disease subgroups The remainder of the hemodynamics are shown in Table I

Patients with predominant aortic regurgitation There were 31 patients in this group 23 men and eight women Eleven patients (35 5%) had associated coronary artery disease and 20 patients (64 5%) did not The ages of patients in the coronary artery disease subgroup ranged from 43 to 76 years (mean age 55 5 ± 7 4 years) and in the non coronary artery disease subgroup ages ranged from 46 to 71 years (mean age 54 5 ± 8 7 years) One vessel disease was present in four patients (36%) and two vessel disease was present in seven patients (64%) No patient had three vessel disease Chest pain was present in nine patients (typical angina seven atypical chest pain two) and in 11 patients (typical angina one and atypical chest pain 10) in the coronary artery disease and noncoronary artery disease subgroups respectively

Risk factors for coronary artery disease were present in nine patients (82%) in the coronary artery disease subgroup and in 16 patients (80%) in the non coronary artery disease subgroup

Exertional dyspnea was present in four patients (36%) with coronary artery disease and in 15 patients (75%) without Syncope did not occur in any of the patients with coronary artery disease but it did occur in six patients (30%) without coronary artery disease

Calcification of the aortic valve was present in four patients (36%) in the coronary artery disease subgroup and in five patients (25%) in the non coronary artery disease subgroup There were no significant differences in the mean pressure gradient across the aortic valve in the coronary artery and non coronary artery disease subgroups The end-diastolic pressure of the left ventricle was 27 ± 13 8 mm Hg in the coronary artery disease subgroup and 19 ± 10 mm Hg in the non coronary artery disease subgroup The cardiac index was 2.5 ± 0 4 L/min/M² and

artery disease The group with aortic regurgitation had one or two vessel disease This may explain why 83% of the patients with aortic stenosis had typical angina in contrast to 64% of patients with aortic regurgitation Although Linhart and colleagues[14] suggested that patients with *aortic regurgitation may be less prone to develop* coronary artery disease the less extensive disease in the patients with aortic regurgitation in our group may in part be explained by the fact that the patients were almost 10 years younger than patients with aortic stenosis (mean age aortic stenosis 65 ± 10 1 years vs aortic regurgitation 55 5 ± 7 4 years) It is of interest also to note that one vessel disease was present in 29% of the 35 patients with aortic valve disease in contrast to 21% with one vessel disease of all the patients with coronary artery disease referred for coronary arteriography in our laboratory

Similar findings of a low incidence of multivessel disease were reported by Graboys and Cohn [13] The prevalence of coronary artery disease in our patients with typical angina pectoris was 77% in contrast to patients with atypical chest pain with only a 25% rate of coronary artery disease ($\underline{P} = 0\,001$) These findings agree with those of Paquay and associates [26] who reported that in patients with aortic valve disease the more typical the angina the more likely these patients are to have coronary artery disease Hancock,[9] in the most recent report of his experience with a large series of patients with aortic stenosis commented on the significance of angina associated with dyspnea He reported that angina occurring on exertion in the absence of dyspnea or occurring at rest with emotional stress after meals or during sleep was associated with coronary artery disease in 80% of instances whereas angina occurring only in association with dyspnea on exertion was associated with coronary artery disease in 45% of instances

An important group of aortic valve disease *patients are those with coronary artery disease* who did not have angina pectoris Only two (6 6%) of our 30 patients without chest pain had coronary artery disease The reported incidence of coronary artery disease in the absence of angina pectoris varies widely Graboys and Cohn [3] found 4% of patients with aortic valve disease to have associated coronary artery disease in the absence of angina pectoris Similarly Paquay and coworkers [4] found coronary artery disease in one of 19 patients (5%) and Bonchek and colleag[ues] found no coronary artery disease among [...] patients with aortic valve disease in the absen[ce] of angina pectoris Harris and associates a[nd] Thompson and co workers[15] reported an inci[...] dence of 10% and 13% (respectively) of corona[ry] *artery disease in patients with aortic valve disea[se]* in the absence of angina pectoris Hancock[9] su[g]gested that patients with aortic valve disease a[nd] coronary artery disease in the absence of angi[na] pectoris may present with symptoms of hea[rt] failure This type of patient may be similar [to] those with ischemic cardiomyopathy in t[he] absence of aortic valve disease as described [by] Burch and associates [29] The hemodynamics in t[he] three groups of patients are shown in Table I[...]

The mean pressure gradient across the aort[ic] valve in patients with aortic stenosis tended to [be] lower in patients who also had coronary arte[ry] disease There were no significant differences [in] left ventricular end diastolic pressure in the su[b]groups of patients with aortic stenosis and coro[...]nary artery disease or no coronary artery disea[se] However in the groups with aortic regurgitati[on] and mixed aortic stenosis aortic regurgitation t[he] left ventricular end diastolic pressure was high[...] in the subgroups of patients with associat[ed] coronary artery disease There were no significa[nt] differences in the cardiac index between the d[if]ferent groups of patients

Comparing the ejection fraction in patie[nts] with coronary artery disease in the differe[nt] groups we found significantly higher ejecti[on] fractions in patients with aortic stenosis rath[er] than in patients with aortic regurgitati[on] ($\underline{P} = 0\,001$) or mixed aortic stenosis aortic reg[ur]gitation ($\underline{P} = 0\,05$) There was no significant d[if]ference in ejection fraction between the aor[tic] regurgitation group and the mixed aortic steno[sis] aortic regurgitation group There was also [...] significant difference in the ejection fraction [...] the patients without coronary artery disea[se] between the different groups

Calcification of the aortic valve was much mo[re] common in the groups with aortic stenosis a[nd] mixed aortic stenosis aortic regurgitation Dy[sp]nea on exertion (Class III or IV New York Hea[rt] Association) was much more common in patie[nts] with mixed aortic stenosis aortic regurgitatio[n] Syncope was present in the coronary artery d[is]ease and no coronary artery disease subgroups [...] patients with aortic stenosis however it occurr[...]

dient across the aortic valve was 65 ± 23.8 mm Hg, the aortic valve area was 0.27 ± 0.07 cm / M², the left ventricular end-diastolic pressure was 34 ± 10.3 mm Hg, the cardiac index was 2.1 ± 0.6 L/min/M², and the left ventricular ejection fraction was 50 ± 13%. In the subgroup without coronary artery disease, the mean systolic pressure gradient across the aortic valve was 67 ± 24 mm Hg. The left ventricular end-diastolic pressure was 22 ± 13 mm Hg, the cardiac index was 2.4 ± 0.4 L/min/M, and the left ventricular ejection fraction was 57 ± 19%.

Discussion

Angina pectoris is a well recognized symptom of patients with significant aortic valve disease in the absence of coronary artery disease. The mechanisms responsible for angina pectoris in aortic valve disease can be explained on the basis of an imbalance between myocardial oxygen supply and demand.[1, 3, 19, 22] Fallen and associates demonstrated that patients with severe aortic stenosis but no demonstrable obstructive coronary artery disease have relatively fixed coronary flow response to catecholamine administration stress, resulting in abnormal myocardial metabolism and ischemia. A fixed coronary flow and decreased myocardial oxygen supply result from the fixed stenotic valve orifice and the low mean aortic pressure.

Other factors that may cause decreased oxygen supply to the myocardium in patients with aortic stenosis are the prolonged ejection time, which, if combined with the tachycardia of exercise, results in a decreased diastolic filling period, the increased left ventricular wall tension,[7, 3] the increased left ventricular mass, and the abnormal flow patterns in the aortic root.[2] Increased myocardial oxygen demand may result from myocardial hypertrophy and increased wall tension due to elevated left ventricular end-diastolic pressure. In patients with aortic regurgitation, angina may be due to an increase in wall tension secondary to increased left ventricular volume and to the lower coronary perfusion pressure during diastole. The presence of significant coronary artery disease in patients with aortic valve disease is an additional, critically important single factor causing angina pectoris.

There is wide variation in the reported prevalence of angina pectoris in patients with significant aortic valvular disease, ranging from 40 to 80% for predominant aortic stenosis[5] and 3 to 30% for predominant aortic regurgitation.[24] Similarly, the prevalence of coronary artery disease in aortic valve disease has been reported to be within a wide range between 20 and 63%.[10, 13, 4, 8] This wide variation in the prevalence of angina and coronary artery disease in patients with aortic valve disease may be a result of differences in the ages of the patients studied and the variable criteria used by different investigators in defining significant coronary artery stenosis. Some authors[1, 13, 2, 2] have used a criterion for significant stenosis lumen narrowing of at least 70 to 75%, but others[14, 3] have used as significant lumen narrowing of ≥ 50%. There is general agreement that in patients without aortic valve disease a lumen narrowing of 70 to 75% is probably needed to cause reduction of coronary flow; however, we agree with Hancock,[8] with Linhart and colleagues,[4] and with Moraski and associates that in patients with significant aortic valve disease a lumen narrowing of ≳ 50% can cause significant hemodynamic abnormalities in the coronary circulation.

The rate of chest pain in our total group of 90 patients was 66%, whereas the rate of coronary artery disease in the same group was only 39%. This indicates that chest pain is not related to coronary artery disease in more than half of the patients with aortic valve disease. However, when aortic valve disease was associated with coronary artery disease, the rate of chest pain was 94%.

The higher incidence of chest pain in patients with aortic valve disease and associated coronary artery disease as compared with patients without coronary artery disease is expected, since both diseases have an additive effect upon ischemia. Of the 55 patients with aortic valve disease but no associated coronary artery disease, eight patients (16%) had typical angina pectoris, 19 patients (35%) had atypical chest pain, and 28 patients (49%) had no chest pain.

The distribution of coronary artery disease in the three groups of patients was 46% in predominant aortic stenosis, 35% in severe aortic regurgitation, and 30% in the mixed aortic stenosis-aortic regurgitation group. Although the rate of coronary artery disease in predominant aortic stenosis was higher than in the aortic regurgitation or mixed aortic stenosis-aortic regurgitation groups, the difference was not statistically significant.

The group with predominant aortic stenosis had more severe disease involving multiple vessels and included three patients with left main

Site of origin of ventricular premature beats in patients with mitral valve prolapse

Edgar Lichstein M D F A C C
Brooklyn N Y

Mitral valve prolapse is a common abnormality,[1] and is frequently associated with ventricular premature beats (VPB) Although malignant ventricular arrhythmia and sudden death are rare [3] they have been reported[4] and are a cause for concern Many features of VPBs have been analyzed in an attempt to predict which may have malignant characteristics and a poor prognosis The site of origin of a VPB is thought to correlate with underlying cardiac pathology and perhaps with prognosis

This study examines the vectorcardiogram of VPBs in ten patients with mitral valve prolapse These VCG loops were then used to postulate the site of origin and attempt to relate this with the type of prolapse and the possible etiology of the VPB

Methods

The study population consisted of 10 patients with mitral valve prolapse diagnosed in our Echocardiographic Laboratory There were two males and eight females with a mean age of 29 1 ± 11 1 years All patients had a midsystolic click and a mid or late systolic murmur Although some of the patients had atypical chest pain none had typical clinical features or ECG evidence of coronary heart disease Three patients had complete cardiac catheterization which confirmed the presence of mitral valve prolapse and the absence of coronary artery disease

Echocardiograms were performed on a Unirad 100 series Echoscope Standard scanning techniques were used

Vectorcardiograms (VCGs) were performed on an Instruments for Cardiac Research Model VCG 1V Vectorcardiograph This system allows the vector loop to be interrupted 400 times per second The Frank Lead System was used for vectorcardiograms of both the normal QRS and the ventricular premature beat All 10 patients were having unifocal ventricular premature beats After the vector of the normal QRS was recorded, the patients were monitored through the VCG unit until a ventricular premature beat occurred The ventricular premature beat was stored in the machine s memory and then all three vector loops were inscribed from the same ectopic beat

Results

The direction of the mean vector of the ventricular premature beat in both the frontal and horizontal plane for all 10 patients is shown graphically in Fig 1 The rotations of the vector loops the type of mitral valve prolapse and the proposed site of origin of the ventricular premature beat are shown in Table I

Fig 2 shows the standard 12 lead electrocardiogram from patient No 9 This 16 year old female presented because of palpitation and was found to have a typical midsystolic click and midsystolic murmur The electrocardiogram shows sinus rhythm with ventricular premature beats and is otherwise within normal limits Fig 3 shows this patient s echocardiogram demonstrating prolapse of the posterior leaflet of the mitral valve Fig 4 shows the vectorcardiogram performed on this patient s ventricular premature beat

Discussion

Mitral valve prolapse is a common abnormality especially in the younger population Auscula

From the Division of Cardiology Maimonides Medical Center State University of New York Downstate Medical Center Brooklyn N Y

Recei ed for publication March 3 1980
Accepted for publication Apr 7 1980

Reprint requests Edg r Lichstein M D Di is on of Cardiology Maimonides Medical Center 480? Tenth Ave Bro klyn N Y 11219

0002-8703/80/100450 + 08$00 80/0 © 1980 The C V Mosby Co

only in patients without coronary artery disease in both groups of aortic regurgitation and mixed aortic stenosis aortic regurgitation This is a surprising finding but it should be interpreted with caution since the number of patients under analysis was small

There was electrocardiographic evidence of myocardial infarction present in two patients with and in two patients without coronary artery disease in the group with aortic stenosis Myocardial infarction which is rare in the absence of obstructive coronary artery disease was reported to occur in patients with aortic stenosis[1] as well as in patients without aortic valve disease and in patients with hypertrophic cardiomyopathy [2]

The etiology of myocardial infarction in patients with aortic stenosis but without significant atherosclerosis is unclear The possible causes are calcific embolus the fact that the increased cardiac mass may have been too great for the existent coronary blood supply narrowing of the intramural coronary arteries and brief periods of hypoxia due to transient hypotension Recently it was shown that myocardial infarction may be precipitated by coronary spasm in vessels with or without atherosclerosis[13] There was no statistical difference in the presence of one or more risk factors for coronary artery disease in the different groups of patients

Our study suggests that although patients with aortic valve disease and typical angina pectoris are most likely to have associated coronary artery disease it is not possible to accurately predict this condition by clinical or hemodynamic findings The absence of chest pain excluded associated coronary artery disease in 94% of our patients with aortic valve disease These findings are in some agreement with the findings of several other investigators [25, 2] but considerably different from the findings of others [8, 1, 15, 24] This raises the question once again whether coronary arteriography should be performed routinely in every patient with aortic valve disease undergoing evaluation with cardiac catheterization Linhart and colleagues[14] suggested that coronary arteriography should be performed in all patients undergoing evaluation for aortic valve replacement since they found significant coronary artery disease in 25% of their patients who had no angina pectoris There is general agreement that coronary arteriography should be performed in all patients with angina pectoris when they are evaluated for aortic valve disease The information provided by coronary arteriography may prove to be important with regard to operative risk and long term prognosis when performing coronary bypass at the time of aortic valve surgery[9] There is however disagreement as to whether coronary arteriography should be performed in patients with aortic valve disease without angina pectoris

Some investigators do not recommend routine coronary arteriography in patients with aortic valve disease who do not have angina pectoris [11] This negative recommendation is based on the observation that none of their patients or those reported by others [4, 7] without angina had significant coronary artery disease Other investigators disagree with this point of view and recommend routine coronary arteriography in all patients with aortic valve disease undergoing cardiac catheterization [15, 5] Their reasoning is that patients with aortic valve disease who are free of angina pectoris have a definite albeit small risk of concomitant significant coronary artery disease

Since the combination of aortic valve replacement and coronary bypass surgery seems to lower the risk of operative morbidity and mortality in aortic valve replacement and improves the long term prognosis we agree with those who advocate routine coronary arteriography for all patients over the age of 40 even if they do not have angina pectoris Another reason for routine coronary arteriography in patients studied for aortic valve replacement is to rule out anomalous aortic origin of coronary arteries These anomalies occur in 0 6 to 1 2% of the total patients undergoing coronary arteriography and are more common in patients with valvular disease[3] Knowing the presence of anomalous origin or the course of a coronary artery may avoid injury to the vessel during aortic valve replacement or may exclude the anomalous vessel from perfusion if this technique is used to perfuse the myocardium during extracorporeal circulation

Summary

We studied the clinical hemodynamic and angiographic findings of 90 consecutive patients with significant symptomatic aortic valve disease 40 years of age or older to evaluate the prevalence of angina pectoris in relation to coronary artery disease and the effect upon cardiac function

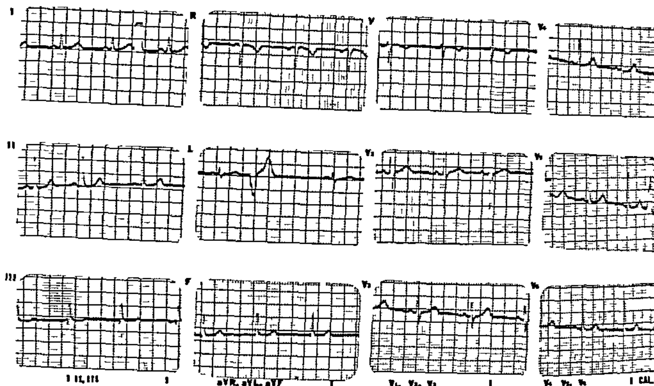


Fig 2 Standard 12 lead electrocardiogram recorded on patient No 9 The rhythm is normal sinus with an occasional ventricular premature beat The QRS morphology is within normal limits

lapse both using Holter monitoring and exercise testing Despite this apparent cause and effect relationship Shappel and Marshall[4] have reported two patients with sudden death and mitral valve prolapse who showed no documented arrhythmia despite extensive ECG and maximum exercise testing Lichtman and co workers[14] have noted a high prevalence of sinus bradycardia and sinus arrest and suggest that this might be one possible mechanism for sudden death

Since most investigators do feel that there is some relationship between verticular arrhythmia and sudden death the mechanism of ventricular irritability becomes important in planning preventive therapy Criley and colleagues[15] postulated that during systole the mitral leaflets become progressively inflated and thus are exposed to an abnormal stress as they balloon into the left atrium tugging on the chordae and papillary muscles During early diastole the leaflets now above the level of the mitral annulus abruptly dump the blood contained within their ventricular aspect into the base of the left ventricle This impact may produce a mechanical stimulus for producing a ventricular ectopic beat This hypothesis however does not account for the intermittent nature of this arrhythmia Micro electrode studies in monkeys and dogs have fou that muscle fibers situated in the mitral val leaflet are capable of developing spontaneo diastolic depolarization resulting in automat impulse initiation when stretched or exposed epinephrine[16, 17] Muscle bundles with accor panying muscular vessels are known to en normally in the mitral leaflet of man[18] Therefor in addition to possible mechanical stimulation the myocardium by excessive movement of th mitral valve leaflet a functional anatomic bas for arrhythmias associated with mitral valve pro lapse syndrome may be ectopic impulse initiatio that occurs in the valve leaflet muscle bun dles[19]

At the present time antiarrhythmic therapy i suggested only when the patient is bothered b palpitations or when malignant characteristics o VPBs are noted Therapy is usually limited t oral propranolol but may occasionally requir diphenylhydantoin when a prolonged QT interval is noted Propranolol may be the drug of choice since in addition to its intrinsic antiarrhythmic action it decreases left ventricular contractility increases left ventricular volume and therefore may lessen myocardial ischemia resulting from excessive traction on the papillary muscle[20] A

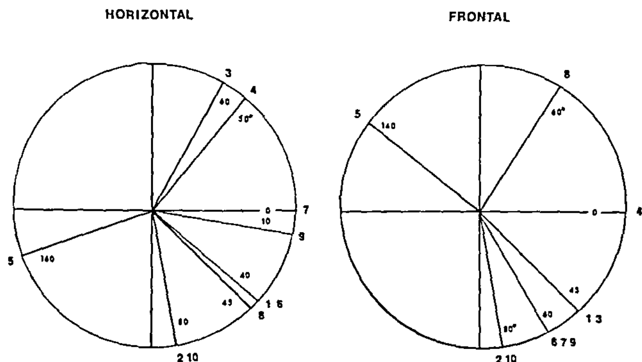


Fig 1 Graphic representation of the mean QRS vector of the ventricular premature beats in all 10 study patients. *The numbers on the outer circumference* identify the study patient both in the frontal and horizontal plane

Table I

Pt no	Age	Sex	*Horizontal* Rotation	*Horizontal* Mean QRS	*Frontal* Rotation	*Frontal* Mean QRS	Prolapse	Origin of VPB
1	26	F	CW	+40	CW	+45	post	LV posterobasal
2	26	F	CW	+80	CW	+80	post	LV posterobasal
3	31	M	CCW	−60	CCW	+45	post	RV anterobasal
4	19	F	CCW	−50	CW	0	post.	RV free wall
5	47	F	CW	+160	CCW	−140°	post	LV posteroapical
6	30	F	CCW	+40	CCW	+60	post	LV posterobasal
7	27	M	CCW	0	CCW	+60	post & ant	LV posterobasal
8	49	F	CCW	+45	CCW	−60	post & ant	LV posteroapical
9	16	F	CCW	+10	CW	+60	post	LV posterobasal
10	20	F	CW	+80	CW	+80	post. & ant	LV posterobasal

Abbreviations CW = clockwise CCW = counterclockwise

tory and echocardiographic features of mitral prolapse may be seen in asymptomatic populations with an incidence ranging from 6 3% to nearly 18% One of the major clinical concerns with this abnormality is the high incidence of ventricular arrhythmia and the occasional occurrence of sudden death

It is thought that there is some relationship between sudden death and the previous occurrence of ventricular premature beats Winkle and associates studied seven patients with prolapse who survived one or more episodes of life threatening ventricular arrhythmias VPBs were present in the ECG of six of the seven and were frequent during exercise testing and Holter monitoring Wei and colleagues[6] described 10 patients with mitral valve prolapse among a larger group of patients with refractory ventricular arrhythmia Four of these patients with prolapse had a history of cardiac arrest due to ventricular fibrillation Other investigators[3, 11] have noted frequent VPBs in patients with mirtal valve pro









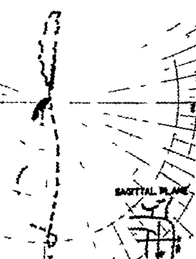


Fig 4 Vectorcardiogram of a ventricular premature beat recorded in patient No 9 The vector loop is interrupted 400 times per second.

superiorly in the frontal plane are thought to arise from the posterior wall of the left ventricle and those that are directed inferiorly arise from the anterior wall of the left ventricle VPBs arising from the base of the left ventricle would have forces directed anteriorly inferiorly and to the left They would be superior or inferior depending on whether the VPB arises from the posterior or anterior wall. Beats arising from the apex of the left ventricle would be directed posteriorly superiorly and to the right All beats originating in the right ventricle had a left bundle pattern The majority were directed inferiorly and to the right Rosenbaum felt that they arose from the anterior wall of the right ventricle and not from the septum They originate in the myocardium and not the Purkinje tissue since the inscription of the initial part of the QRS is slow He felt that they may arise from the anterior papillary muscle of the right ventricle and that perhaps the stretching of that structure during normal mechanical activity of the ventricle could trigger ventricular premature beats.

Using this type of classification Hiss and colleagues[8] evaluated VPBs in a population of healthy male subjects of various ages They found that the number of VPBs from the right ventricle were approximately three times as great as those from the left The incidence of VPBs from the right ventricle increased fourfold from the youngest to the oldest age group (20 to 45+ years) while the rate for those originating in the left ventricle did not change significantly

If one accepts this type of classification for the purpose of determining origin then the significance of this site of origin must be examined. The coronary drug project data showed an increased mortality rate in patients with VPBs following myocardial infarction However these investigations found that this excess risk was associated

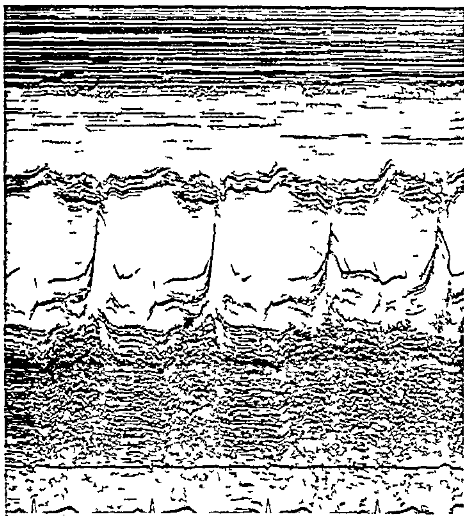


Fig 3 Echocardiogram recorded on patient No 9 *The arrow* indicates late systolic prolapse of the posterior leaflet of the mitral valve

radical and seldom used method of therapy is mitral valve replacement which occasionally has been thought to be necessary for the prevention of recurring life threatening arrhythmia [21] More recently aprindine has been used Troup and Zipes [2] describe the use of this drug in seven patients with symptomatic potentially life threatening ventricular arrhythmias Conventional antiarrhythmic drugs had been tried and were unsuccessful Aprindine resulted in a greater than 91% reduction in the number of VPBs in 24 hours in addition to a marked reduction in the frequency and duration of ventricular tachycardia

VPBs may be found in all age groups even in the absence of cardiac disease Since they are so common many have attempted to find characteristics which differentiate benign from malignant VPBs Rosenbaum using electrocardiograms from humans has classified ventricular extrasystoles according to their form and their site of origin Mautner and Girotti [4] arrived at a similar classification using pacemaker induced ventricular beats in the experimental dog It becomes apparent from these studies that one cannot simply identify the site of origin by merely noting the presence of a classical right bundle or left bundle pattern in the frontal plane Manning and colleagues[25] have noted a common discordance between the findings in the limb and the precordial leads Because of this a determination must be made by seeing the same VPB in both the frontal and horizontal plane or by the use of the vectorcardiogram Rosenbaum s classification[21] states that VPBs from the left ventricle will have a right bundle pattern Those that are directed

tissue judged by the slow initial forces (3) There was no relationship between the location of prolapse and the VPB morphology

Summary

This study examines the site of origin and possible etiology of ventricular premature beats (VPB) in patients with mitral valve prolapse

Ten patients with mitral valve prolapse documented by echocardiogram form the study group All patients had prolapse of the posterior leaflet and three additionally had anterior prolapse There were eight females and two males, with a mean age of 29 1 ± 11 1 years All patients were having unifocal VPBs at rest A vectorcardiogram (VCG) was taken of the VPB by a technique which allowed all VCG loops to be written from the same beat

The VCG analysis indicated that the VPB forces were directed anteriorly inferiorly and to the left in six patients In two patients the VPB was directed posteriorly inferiorly and to the left consistent with right ventricular origin One of these patients had episodes of ventricular tachycardia One was anterior superior and to the left, and one was markedly anterior superior and to the right In all patients the initial portion of the QRS was inscribed slowly The three patients with additional anterior prolapse did not show a common difference from those with isolated posterior prolapse

It is concluded that (1) The majority of these VPBs originate from the posteriorbasal portion of the left ventricle (2) They originate in the myocardium and not in the Purkinje tissue (3) There is no relationship between the location of prolapse and the VPB morphology

I wish to thank Ms Carol Scott for her assistance in preparing the manuscript and Dr Prem K. Gupta for performing the echocardiograms

REFERENCES

1 Barlow J B and Pocock W A Mitral valve prolapse the specific bill wing mitral leaflet syndrome or an insignificant non ejection systolic click AM HEART J 97 277 19 9
2 Swartz, M H Teichholz L E and Donoso E Mitral valve prolapse A review of associated arrhythmias Am J Med. 62 377 19
3 Gooch A S Vicencio F Maranhao V and Goldberg H Arrhythmias and left ventricular asynergy in the prolapsing mitral leaflet syndrome Am J Cardiol 29 611 197?
4 Shappell S D and Marshall C E Ballooning posterior leaflet syndrome Syncope and sudden death, Arch Intern Med 135 664 1975
5 Winkle R A. Lopes M G Fitzgerald, J W Goodman D J Schroeder J S and Harrison D C Arrhythmias in patients with mitral valve prolapse Circulation 52 73, 1975
6 Wei J Y Bulkley B H., Schaeffer A H Greene H.L., and Reid P R Mitral valve prolapse syndrome and recurrent ventricular tachyarrhythmias A malignant variant refractory to conventional drug therapy Ann Intern Med 89 6 1978
7 Shappell S D Marshall C E Brown, R E and Bruce T A Sudden death and the familial occurrence of mid systolic click, late systolic murmur syndrome Circulation 48 1128 1973
8 Barlow J B Bosman C K and Pocock, W A. Late systolic murmurs and non ejection (mid late) systolic clicks Br Heart J 30 203 1968
9 Hancock E W and Cohn K The syndrome associated with mid systolic click and late systolic murmur Am J Med 4 183 1966
10 Jeresaty R M The syndrome associated with mid systolic click and/or late systolic murmur Chest 59 643, 1971
11 Winkle R A Lopes M G Popp R L., and Hancock, E W Life threatening arrhythmias in the mitral valve prolapse syndrome Am J Med 60 961 1976
12 DeMaria A N Amsterdam E A. Vismara L. A. Neumann A and Mason D T Arrhythmias in the mitral valve prolapse syndrome Prevalence nature and frequency Ann Intern Med 84 656 1976
13 Sloman G Wong M and Walker J Arrhythmias on exercise in patients with abnormalities of the posterior leaflet of the mitral valve AM HEART J 83 31? 1972
14 Leichtman D Nelson R Gobel, F L. Alexander C.S., and Cohn J N Bradycardia with mitral valve prolapse A potential mechanism of sudden death Ann Intern Med 85 453 1976
15 Criley J M Zeilenga D W and Morgan M T Mitral dysfunction A possible cause of arrhythmias in the prolapsing mitral leaflet syndrome Trans Am Clin Climatol. Assoc 85 44 1973
16 Wit A L. Fenoglio J J Wagner B M and Bassett, A L Electrophysiological properties of cardiac muscle in the anterior mitral valve leaflet and the adjacent atrium in the dog Circ Res 32 731 1973
17 Wit A L and Cranefield P F Triggered activity in cardiac muscle fibers of the simian mitral valve Circ Res 38 85 1976
18 Montiel M M Muscular apparatus in the mitral valve in man and its involvement in left sided cardiac hypertrophy Am J Cardiol 26 341 1970
19 Aranda J M Befeler B El Sherif N Castellanos A and Lazzara R Mitral valve prolapse Am J Med 60 997 1976
20 Jeresaty R M Sudden death in the mitral valve prolapse-click syndrome Am J Cardiol. 37 317, 1976
21 Cobbs B W and King S B Mechanism of abnormal ventriculogram associated with prolapsing mitral valve (Abstr) Circulation 49 and 50 (Suppl III) III 7 1974
22 Troup P J and Zipes D P Aprindine treatment of recurrent ventricular tachycardia in patients with mitral valve prolapse AM HEART J 97 3?? 1979
23 Rosenbaum M B Classification of ventricular extrasystoles according to form J Electrocardiol. 2 2?? 1969
24 Mautner B and Girotti A. L Premature ventricular beats Experimental study AM HEART J 85 3?? 1973
25 Manning G W Ahuja S P and Gutierrez, V R

with frequency of VPBs but was independent of ECG criteria such as whether the VPBs originated in the right or left ventricle Lewis and associates[28] studied 165 patients with VPBs classified as either of right or left ventricular origin Patients with no heart disease had a higher incidence of right ventricular VPBs Of 102 patients with left ventricular disease 51% had left ventricular VPBs Of the six patients with right ventricular disease five of six (83%) had right ventricular VPBs These authors concluded that patients with right ventricular disease generally had right ventricular VPBs In patients with left ventricular disease the incidence of left ventricular and both right and left ventricular VPBs was much higher than in patients with right ventricular disease alone Kennedy and Underhill studied 25 asymptomatic healthy patients because of frequent or complex VPBs These beats were classified by ECG and in 10 vector criteria were also used The beats were predominantly of right ventricular origin in 19 of 25 subjects and disappeared during exercise in 21 of 23 subjects Three of the 10 subjects classified by vector criteria had beats which were thought to originate in the left ventricle but were still thought to be benign Pietras and colleagues[30] studied 27 patients with chronic recurrent ventricular tachycardia Fifteen had left ventricular tachycardia and all had organic heart disease There were 12 with right ventricular tachycardia and they were younger mostly female and only three had organic heart disease During follow up there were three deaths and these were all in the group with left ventricular tachycardia These authors mention that one patient had a pansystolic murmur but they do not document the diagnosis of mitral prolapse in any of these patients It is of interest to note that one of our patients (patient No 3) had ventricular tachycardia during an exercise test which required DC cardioversion This patient s VPBs and his ventricular tachycardia were both consistent with right ventricular origin

Because of this proposed relationship between the site of origin and the presence of disease removal of disease such as left ventricular aneurysm has been suggested for recurrent ventricular tachycardia While this may be successful [31] it is also reported that patients with right ventricular tachycardia may also improve after left ventricular aneurysmectomy [3] Tomisawa and co workers[33] described one patient with right ventricular tachycardia which was abolished by right ventricular aneurysmectomy and Engle and associates[5] describe two children with left ventricular tachycardia which was abolished by excision of a left ventricular tumor With the exception of the rare patients with right ventricular tachycardia and left ventricular aneurysmectomy these data are though to validate the proposed ECG localization of ventricular tachycardia [30] Bodenheimer and colleagues[3] studied 39 patients with VPBs who had cardiac catheterization Nineteen had left ventricular VPBs 17 had right ventricular VPBs and three had both left and right ventricular VPBs Of the 19 with left ventricular VPBs 15 had coronary disease and four were normal Of the 17 with right ventricular VPBs 11 had coronary disease and six were normal The three patients with both left and right VPBs also had coronary disease These findings indicate that in patients with chest discomfort syndrome there was no relationship between site of origin of the VPB and either the prevalence or the severity of coronary disease These authors note that the Purkinje fibers penetrate the interventricular septum for a considerable distance from the left ventricle towards the right ventricle Thus an impulse originating from the left ventricular portion of the septum could depolarize the right ventricle first These authors suggested that this might explain the presence of right ventricular VPBs in three patients with isolated disease of the left anterior descending coronary artery

We classified the origin of VPBs using vector cardiographic criteria suggested by Sano and co workers Using these criteria it was felt that only two patients had VPBs originating in the right ventricle and the remaining eight had VPBs originating in the left ventricle The most common site of origin was the posteriorbasal portion of the left ventricle This is perhaps consistent with the hypothesis that mechanical irritation produced by the billowing valves dumping blood into the left ventricle could be the cause of this arrhythmia A possible origin from the base of the papillary muscles seems unlikely, since that origin would have been expected to produce a superiorly oriented electrical force while ours were mostly inferiorly directed

From this study we conclude that (1) The majority of these VPBs originate from the posteriorbasal portion of the left ventricle (2) They originate in the myocardium and not the Purkinje

Cardiovascular manifestations of tricyclic antidepressant overdose

Rene A Langou M D
Craig Van Dyke M D
Steven R Tahan M D
Lawrence S Cohen M D
New Haven Conn

Cardiotoxicity in tricyclic overdosage has been reported frequently during the last 15 years Most studies[1] have focused attention on the characteristic pattern of electrocardiographic disturbances which as Giles pointed out is so constantly seen as to be pathognomonic Little clinical information however regarding the broader aspects of the effects of tricyclic overdose upon the cardiovascular system has been accumulated

We have recently reported on clinical findings of patients with tricyclic antidepressant (TCA) overdoses and their correlations with (TCA) plasma levels Our present study will concentrate only on the cardiovascular manifestations of TCA overdose We present the results of a retrospective analysis of the cardiac manifestations of 35 cases of TCA overdosage 23 cases with amitriptyline and 12 cases with imipramine

Materials and methods

The clinical histories of 23 cases of amitriptyline overdose and 12 cases of imipramine overdosage admitted to Yale New Haven Hospital from January 1973 to December 1978 were reviewed The criteria for inclusion in this study were history of tricyclic antidepressant overdose and elevated plasma levels of TCA [9] Patients who were known to have ingested significant amounts of drugs other than TCA were excluded from the study

The patients ranged in age from 13 to 73 years eight patients were teenagers Twenty seven patients were female and eight patients were male There was no previous history of cardiac disease in any case Twenty patients were receiving TCA drugs chronically

The clinical protocol followed in each one of the 35 patients after admission to the intensive care unit at Yale New Haven Hospital was physical examination routine laboratory and toxicologic determinations electrocardiograms and routine chest x rays In five patients right sided heart pressures and cardiac output by thermodilution technique were sequentially measured through a Swan Ganz catheter placed in the pulmonary circulation using standard techniques [10] In addition determination of plasma levels of TCA and their respective active metabolites were obtained Initial blood samples for tricyclic levels were obtained within 2 to 4 hours after admission to the intensive care unit In addition levels were determined at variable intervals thereafter Plasma concentrations of the parent compounds amitriptyline and imipramine and their respective pharmacologically active metabolites nortriptyline and desmethylimipramine were measured by gas liquid chromatography using a nitrogen sensitive detector accord

From the Department of Internal Medicine Cardiology Section and Department of Psychiatry Yale University School of Medicine New Haven, Conn.

Received for publication Mar 28 1980
Accepted for publication May 5 1980

Reprint requests Rene A. Langou M.D Cardiology Section Yale University School of Medicine 333 Cedar St., 87 LMP New Haven, Conn. 06510

000_ 8703/80/100458 + 0/00 0/0 © 1980 The C V Mosby Co.

Electrocardiographic differentiation between ventricular ectopic beats from subjects with normal and diseased hearts Acta Cardiologica 23 462 1968
26 Hiss R G Averill K H and Lamb L E Electrocardiographic findings in 67,375 asymptomatic subjects Am J Cardiol 7 96 1960
27 The Coronary Drug Project Research Group Prognostic importance of premature beats following myocardial infarction Experience in the coronary drug project J.A.M.A. 223 1116 1973
28 Lewis, S Kanakis C Rosen K M and Denes P Significance of site of origin of premature ventricular contractions, Am Heart J 97 159 1979
29 Kennedy H L and Underhill S J Frequency of complex ventricular ectopy in apparently healthy subjects A clinical study of 25 cases, Am J Cardiol 38 141 19 6
30 Pietras R J Mautner R Denes P Wu D Dhingra R. Towne W and Rosen K Chronic recurrent right and left ventricular tachycardia Comparison of clinical hemodynamic and angiographic findings, Am J Cardiol 40 32 1977
31 Thind U S Blakemore W S and Zinsser H F Ventricular aneurysmectomy for the treatment of recurrent ventricular tachyarrhythmia Am J Cardiol. 27 690 1971
32 Hunt D Sloman G and Westlake G Ventricular aneurysmectomy for recurrent tachycardia Br Heart J 31 264 1969
33 Tomisawa M., Onouchi Z and Goto M Right ventricular aneurysm with ventricular premature beats, Br Heart J 36 1182 1974
34 Engle M A Ebert P A and Redo S F Recurrent ventricular tachycardia due to resectable cardiac tumor Circulation 50 1052 1974
35 Bodenheimer M M Banka V S and Helfant R. H Relationship between the site of origin of ventricular premature complexes and the presence and severity of coronary heart disease Am J Cardiol. 40 865 1977
36 Sano T Hiroki, T and Suzuki, F The vectorcardiogram of ventricular premature beats An analysis of vectorcardiograms from 100 cases taken by Frank s method Jap Heart J 8 388 1967

Copyright Information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner s consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients This consent is given on the condition however that the copier pay the stated per copy fee through the Copyright Clearance Center Inc 21 Congress Street Salem Mass 01970 617 744 3350 for copying beyond that permitted by Sections 107 or 108 of the U S Copyright Law This consent does not extend to other kinds of copying such as copying for general distribution for advertising or promotional purposes for creating new collective works or for resale For reprint quantities of 50 or more contact Publisher

Table II Electrocardiographic manifestations of tricyclic antidepressant overdose in 35 patients

	Number	*Per cent*
Sinus tachycardia	25	71
Supraventricular tachycardia	2	6
Premature ventricular beats	12	34
Prolongation of PR interval	4	11
Prolongation of QRS complex	10	29
Right bundle branch block	5	
Intraventricular conduction delay	5	
Abnormal ST segment	10	28
Abnormal T wave	10	28
Prolongation of QT interval	30	86
Normal electrocardiogram	7	20

sions of normal saline solution (1 5 ± 0 7 liters) in an average of 3 hours After fluid infusion the following hemodynamic measurements were obtained—heart rate 118 ± 12 beats per minute pulmonary capillary wedge pressure 12 ± 3 mm Hg mean pulmonary artery pressure 18 ± 6 mm Hg systemic systolic blood pressure 82 ± 12 mm Hg and cardiac output 4 8 ± 0 5 mm Hg After fluid infusion in these five patients right sided and left ventricular filling pressures were normalized and cardiac output was significantly increased A small but statistically significant rise in systolic blood pressure was also observed However no change in heart rate was noted after the therapeutic intervention The systemic hypotension was finally corrected in these five particular patients with the infusion of sympathomimetic amines Of note is that the heart rate remained elevated despite complete correction of all measured hemodynamic parameters (118 ± 10 beats/minute)

Electrocardiographic manifestations on admission Of the 35 patients with amitriptyline or imipramine overdose sinus tachycardia was documented in 71% (25 of 35) supraventricular tachycardia was found in 6% (two of 35), premature ventricular beats were seen in 34% (12 of 35) prolongation of the PR interval (first degree A V block) was documented in 11% (four of 35) Widening of the QRS complex was observed in 29% (10 of 35) Of these patients with a widened QRS complex five patients had right bundle branch block and five patients had non specific intraventricular conduction delay Abnormal ST segments and T waves were present in 28% (10 of 35) and prolongation of the QT interval was apparent in 86% (30 of 35) (Table II) Seven of the 35 patients had completely normal electrocardiograms

Twelve patients demonstrated severe ventricular ectopy (more than 60 PVC s per hour) in the 12 lead admission electrocardiograms An additional patient developed severe ventricular ectopy upon arrival at the intensive care unit Of these 13 patients 10 patients had uniform PVCs No patients had sustained repetitive ventricular tachyarrhythmias Three of the original 13 patients with severe ventricular ectopy were reported as having a cardiopulmonary arrest prior to admission

The duration of ventricular ectopic activity ranged up to 72 hours after admission but 10 patients did not show any further ventricular ectopy after 36 hours Intravenous infusion of lidocaine (2 0 ± 0 5 mg/minute mean ± SD) was used to control the frequent premature ventricular beats in all 13 patients The use of this antiarrhythmic agent did not produce any detectable undesirable rhythm disturbances After transfer from the intensive care unit to regular medical wards none of these patients were found to have arrhythmias Long term Holter monitor tracings were obtained in all of these patients Only one had severe ventricular ectopy (multiform premature ventricular beats) in the first Holter monitor tracing (72 hours after admission) which disappeared in the second Holter monitor recording (before discharge) Two patients had nonsevere ventricular ectopy in the first Holter monitor recording which also disappeared at the time of discharge (second Holter monitor recording) No arrhythmias were noted in the Holter tracings of the remaining ten patients

Evolution of abnormal electrocardiographic manifestations Twenty eight patients with abnormal admission electrocardiograms had the following electrocardiographic evolution during their hospital stays Sixteen patients (including five with widened QRS complexes) had their electrocardiogram revert to normal within [illegible] hours after admission The remaining 12 patients demonstrated persistent prolongation of the QT interval at 72 hours following admission

Fig 1 presents the relationship between the duration of the QRS complex and plasma level of imipramine in four patients with widened QRS complexes in which sequential TCA blood levels were available There was a

ing to methods previously reported from our institution [1,2]

The electrocardiographic interpretations were made according to the Minnesota Code[13] for rhythm AV conduction QRS complex and ST and T waves The QT interval was corrected for rate according to the formula of Ashman and associates[14] Electrocardiograms were obtained upon admission to the intensive care unit and thereafter daily until tracings were interpreted to be within normal limits Twenty four hour ambulatory long term electrocardiograms (Holter monitor) were obtained in patients who had ventricular ectopy on admission at 72 to 96 hours after admission and the day before discharge from the hospital (5 to 7 days after admission) The scanning of the Holter monitor tapes was done by a highly trained physician and was reviewed by the staff cardiologist Initially each Holter monitor tape was reviewed at fast speed (60 times real time) using a commercially available scanner When any abnormal rhythm was identified the Holter monitor tape was replayed and the electrocardiogram was recorded in paper at a speed of 25 mm/sec The abnormal rhythm was classified and the number of ectopic beats were manually counted Cardiac arrhythmias were classified as supraventricular tachyarrhythmias ventricular tachyarrhythmias and conduction disturbances Supraventricular tachyarrhythmias were classified as atrial premature beats (>60/hour) atrial flutter and atrial fibrillation Ventricular tachyarrhythmias were classed as (1) severe ventricular ectopy (either premature ventricular contractions (PVC) >60/hour multiform premature ventricular contractions repetitive PVC s or ventricular tachycardia or fibrillation) and (2) nonsevere ventricular ectopy (uniform PVCs at <60/hour) Conduction disturbances were recorded as atrioventricular block and intraventricular block

The medical treatment in this series of 35 patients with tricyclic overdose was supportive only and included intravenous fluids sympathomimetic amines gastric lavage activated charcoal magnesium citrate and support of respiration Hemodialysis and peritoneal dialysis were not used in these patients and all recovered uneventfully

CDC-70 Hittm n Medcraft, Skippa k, Pennsyl ania

Table I Clinical findings in 35 patients with amitriptyline (23 patients) and imipramine (12 patients) overdose

	Number	Per cent
Tachycardia	25	71
Hypotension	18	51
Atrial gallop (S_4)	5	14
Ventricular gallop (S_3)	4	11
Summation gallop ($S_3 + S_4$)	6	17
Ejection systolic murmur	10	28

Plasma levels The total initial plasma levels of amitriptyline plus active metabolites ranged from 180 to 1 560 ng/ml with a mean ± SD of 430 ± 74 ng/ml and plasma levels of imipramine plus active metabolites ranged from 150 to 1 732 ng/ml with a mean ± SD of 665 ± 137 ng/ml

Statistical analysis When appropriate the data were statistically analyzed by unpaired Student t test A p value less than 0 05 was considered as statistically significant

Results

Physical findings The admission clinical findings in the 35 patients with TCA overdose are displayed in Table I Tachycardia (heart rate >110 beats per minute [bpm]) was present in 71% of patients (25 of 35) hypotension (systolic blood pressure <80 mm Hg) was seen in 51% (18 of 35) hypotension occurred more often with amitriptyline overdose (65% 15 of 23) than with imipramine overdose (16% 2 of 12)

Cardiovascular hemodynamic measurements In five patients with marked hypotension and tachycardia a Swan Ganz catheter was placed in the pulmonary artery Heart rate pulmonary capillary and pulmonary artery pressures systemic arterial pressure and cardiac output were sequentially measured These measurements were repeated as clinically indicated during a 24 hour period The initial hemodynamic measurements were heart rate 121 ± 8 beats per minute (mean ± SD) pulmonary capillary wedge pressure 6 ± 3 mm Hg mean pulmonary artery pressure 10 ± 4 mm Hg systemic systolic blood pressure 65 ± 8 mm Hg and cardiac output 2 8 ± 1 2 liters/minute The initial low left ventricular filling pressures (pulmonary capillary wedge pressures) were corrected with infu

Table II Electrocardiographic manifestations of tricyclic antidepressant overdose in 35 patients

	Number	*Per cent*
Sinus tachycardia	25	71
Supraventricular tachycardia	2	6
Premature ventricular beats	12	34
Prolongation of PR interval	4	11
Prolongation of QRS complex	10	29
Right bundle branch block	5	
Intraventricular conduction delay	5	
Abnormal ST segment	10	28
Abnormal T wave	10	28
Prolongation of QT interval	30	86
Normal electrocardiogram	7	20

sions of normal saline solution (1 5 ± 0 7 liters) in an average of 3 hours After fluid infusion the following hemodynamic measurements were obtained—heart rate 118 ± 12 beats per minute pulmonary capillary wedge pressure 12 ± 3 mm Hg mean pulmonary artery pressure 18 ± 6 mm Hg systemic systolic blood pressure 82 ± 12 mm Hg and cardiac output 4 8 ± 0 5 mm Hg After fluid infusion in these five patients right sided and left ventricular filling pressures were normalized and cardiac output was significantly increased A small but statistically significant rise in systolic blood pressure was also observed However no change in heart rate was noted after the therapeutic intervention The systemic hypotension was finally corrected in these five particular patients with the infusion of sympathomimetic amines Of note is that the heart rate remained elevated despite complete correction of all measured hemodynamic parameters (118 ± 10 beats/minute)

Electrocardiographic manifestations on admission Of the 35 patients with amitriptyline or imipramine overdose sinus tachycardia was documented in 71% (25 of 35) supraventricular tachycardia was found in 6% (two of 35), premature ventricular beats were seen in 34% (12 of 35) prolongation of the PR interval (first degree A V block) was documented in 11% (four of 35) Widening of the QRS complex was observed in 29% (10 of 35) Of these patients with a widened QRS complex five patients had right bundle branch block and five patients had non specific intraventricular conduction delay Abnormal ST segments and T waves were present in 28% (10 of 35) and prolongation of the QT interval was apparent in 86% (30 of 35) (Table II) Seven of the 35 patients had completely normal electrocardiograms

Twelve patients demonstrated severe ventricular ectopy (more than 60 PVC s per hour) in the 12 lead admission electrocardiograms An additional patient developed severe ventricular ectopy upon arrival at the intensive care unit Of these 13 patients 10 patients had uniform PVCs. No patients had sustained repetitive ventricular tachyarrhythmias Three of the original 13 patients with severe ventricular ectopy were reported as having a cardiopulmonary arrest pri to admission

The duration of ventricular ectopic activi ranged up to 72 hours after admission but patients did not show any further ventricul ectopy after 36 hours Intravenous infusion lidocaine (2 0 ± 0 5 mg /minute mean ± S was used to control the frequent premature ve tricular beats in all 13 patients The use of tl antiarrhythmic agent did not produce any dete able undesirable rhythm disturbances. Af transfer from the intensive care unit to regu medical wards none of these patients were fou to have arrhythmias Long term Holter monit tracings were obtained in all of these patien Only one had severe ventricular ectopy (mul form premature ventricular beats) in the fi Holter monitor tracing (72 hours after adm sion) which disappeared in the second Holt monitor recording (before discharge) Two p tients had nonsevere ventricular ectopy in t first Holter monitor recording which also disa peared at the time of discharge (second Holt monitor recording) No arrhythmias were not in the Holter tracings of the remaining t patients

Evolution of abnormal electrocardiograph manifestations Twenty eight patients with a normal admission electrocardiograms had the f lowing electrocardiographic evolution dur their hospital stays Sixteen patients (includi five with widened QRS complexes) had th electrocardiogram revert to normal within hours after admission The remaining 12 patien demonstrated persistent prolongation of the Q interval at 72 hours following admission

Fig 1 presents the relationship between t duration of the QRS complex and plasma level imipramine overdose in four patients wi widened QRS complexes in which sequenti TCA blood levels were available There was

progressive normalization of the QRS complex duration while the plasma levels of imipramine were *falling to lower levels The QRS complex* durations were in the normal range when the plasma level of imipramine was below 200 ng/ml

Discussion

The pharmacology of TCA on the cardiovascular system has been extensively studied [13] These drugs have a number of pharmacological actions that include anticholinergic activity direct myocardial depressant activity and a sympathomimetic activity which is related to their ability to block the reuptake of adrenergic amines All of these actions may contribute to the adverse effects of TCA on the cardiovascular system however the individual dose response curves for each of these actions remains undefined A factor further influencing TCA cardiotoxicity is that these drugs are highly concentrated by the myocardium [1]

Cardiovascular findings in TCA overdose The most common cardiovascular signs of TCA overdose in this study were tachycardia (71% 25 of 35 patients) and hypotension (51% 18 of 35 patients) Previous studies [9,1] of therapeutic and/or toxic doses of TCA have demonstrated that tachycardia is a prominent feature This chronotropic effect could be related to several physiologic mechanisms direct stimulation of the sinus node reflex mechanism induced by the clinically significant hypotension or direct effect upon the cardioregulatory center in the central nervous system The tachycardia observed in our patients appeared to be independent of changes in blood pressure The five patients who were invasively instrumented demonstrated no change in heart rate when the blood pressure was restored to normal levels This finding suggested that the tachycardia *cannot be explained by a hypotension* reflex mechanism alone By this study we were not able however to elucidate the operative pathophysiologic mechanism

Hypotension was the second most prominent cardiovascular manifestation of TCA overdose occurring in 51% of all cases The first substantial study of TCA on blood pressure reported no change in recumbent blood pressure but there was a significant frequency of postural hypotension These changes were observed especially in older patients and in patients with organic cardiovascular disease Subsequent studies [3] documented that postural hypotension is independent of age sex and blood levels of TCA The mechanism whereby TCA produces hypotension is unclear [23,6] but it has been attributed to a peripheral effect a myocardial depressant effect a direct effect upon the central nervous system and a combination of these influences

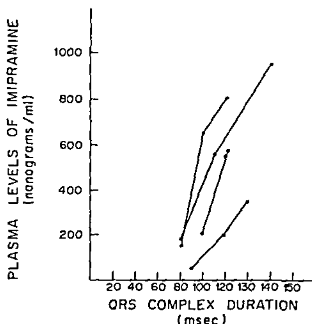


Fig 1 Relationship between plasma levels of imipramine and duration of the QRS complex in four patients with intraventricular conduction defects.

In five hemodynamically monitored patients in our cohort with TCA overdose hypotension was associated with marked intravascular fluid depletion manifested by low left ventricular filling pressures and low cardiac output When left ventricular filling pressures and cardiac output were corrected the blood pressure increased but it still was clinically in the hypotensive range Hemodynamic measurement of cardiac function did not indicate left heart failure These findings suggest a TCA mediated afterload reduction

Thorstrand carefully examined cardiovascular hemodynamics in ten patients who overdosed with TCA using right heart catheterization The hemodynamic data were obtained during and after recovery from coma As judged by the pulmonary arterial diastolic pressure central venous pressure and cardiac output myocardial failure did not occur during overdose in any of these patients

The only other previous attempt to measure

the effects of TCA on left ventricular function in human subjects used systolic time intervals All eight patients in that study had therapeutic levels of TCA An increase in the ratio of pre ejection period over duration of left ventricular ejection time (PEP/LVET) was found in all patients The authors concluded that TCA therapy is associated with a decrement in left ventricular function In interpreting the significance of these results we note that measurements of systolic time intervals may not be adequate to evaluate left ventricular function [29-31]

These two studies have produced contradictory findings on the influence of TCA on left ventricular function The study of Taylor and Braithwaite [8] using therapeutic plasma levels, suggests that these drugs depress left ventricular function Somewhat surprisingly the study of Thorstrand using toxic plasma levels found little effect of TCA on left ventricular function Our findings are in agreement with those of Thorstrand in that TCA at toxic plasma levels did not clinically impair left ventricular function

Electrophysiologic manifestation of TCA overdose The electrophysiologic manifestations of TCA overdose have been reported in detail by several other investigators [3-38] In 1962 Cairncross and Gershon[39] studied imipramine cardiotoxicity in anesthetized cats and dogs These investigators were able to show that increasing doses of intravenous imipramine up to 8 mg/kg produced serious cardiac conduction disturbances which they interpreted as toxic effects on the conduction tissue Boissier and co workers [40] in another experimental study with progressive lethal intoxication in guinea pigs mention that progressively higher degrees of atrioventricular block occurred with increasingly higher doses of TCA and that conduction impairment improved between doses (except when the point of irreversible intoxication occurred when all electrical activity of the heart ceased)

The most characteristic electrocardiographic manifestations found in patients with TCA overdose are conduction and repolarization disturbances atrioventricular block, intraventricular conduction defects T wave changes and prolonged QT interval Tricyclic antidepressants exert a quinidine like action upon the conduction system in all studied species Therefore the toxic manifestations of TCA should be similar to those induced by quinidine toxicity Our study showed a high incidence of conduction impairment in patients with imipramine and amitriptyline overdose prolonged PR interval in 11% prolonged QRS complex in 29% and prolonged QT interval in 86% The pathophysiologic behavior of these conduction disturbances was very similar to that reported in pigs [40]

Of interest is the fact that we did not document ventricular tachycardia in any of our patients, although ventricular tachycardia has been described in the preterminal phase of severe intoxications It is possible that the bizarre wide QRS complexes which are so commonly seen in TCA overdose reflect an aberrantly conducted supraventricular tachycardia rather than ventricular tachycardia Two of our patients, who had a supraventricular tachycardia had very wide and bizarre QRS complexes which reverted to normal when plasma levels of imipramine diminished

It should be noted that no serious ventricular arrhythmia occurred in our patients, and only 13 patients had initial ventricular ectopic activity These ventricular premature beats were treated in the same manner as quinidine-induced ventricular tachyarrhythmias Since the electrophysiologic actions of both quinidine and procainamide are identical to those of TCA it is unlikely that either drug would abolish the ventricular ectopy They may even aggravate the electrophysiologic abnormalities because TCA induced arrhythmias may result from re entrant excitation currents secondary to slowed conduction velocity in the myocardium Lidocaine appears to be the therapeutic drug of choice However abolition of ventricular activity with lidocaine may unmask serious underlying rhythm disorders which might require the placement of a temporary pacemaker In our patients lidocaine infusion was able to control all ventricular ectopic beats without any undesirable effect Thirteen of our patients with initial ventricular ectopy had two (24 hours each) long term Holter monitor recordings only one patient had severe ventricular ectopy and two additional patients had nonsevere ventricular ectopy during the first electrocardiographic recording These three patients were free of ventricular ectopy at the time of the second recording It should be noted that no patients received antiarrhythmic drugs during that late phase of their hospitalization

The relative lack of ventricular arrhythmias in

our cohort was surprising in view of previous reports[13, 36, 3] which suggested a high incidence of malignant arrhythmias with TCA overdose We found no malignant arrhythmias in any of the patients either on admission or during monitoring in the intensive care unit Follow up Holter monitors in 13 of our patients who were felt to be at higher risk showed no ventricular or supraventricular arrhythmias during hospitalization

Clinical implications

This study presented the following relevant clinical cardiovascular information for treating patients with tricyclic antidepressant overdose

1 Tachycardia and hypotension were very frequently found in patients with tricyclic overdose Tachycardia was not solely related to reflex mechanisms induced by systemic hypotension but rather to direct chronotropic effect of tricyclic agents Systemic hypotension was partially related to relative fluid depletion but peripheral vascular mechanisms also played a very important role Cardiac failure was not documented in any of the hemodynamically instrumented patients

2 The most prominent electrophysiologic changes observed appeared to be related to disturbance in conduction and repolarization clinically manifested by AV block intraventricular conduction defects and prolongation of QT interval

3 No malignant rhythm disturbances were seen and the 13 patients with ventricular ectopic activity were successfully treated with lidocaine an antiarrhythmic drug which enhances electrical conduction velocity

Summary

The cardiotoxicity of tricyclic antidepressants (TCA) was studied in 35 patients admitted to Yale New Haven Hospital for an acute overdose 23 patients had amitriptyline overdose and 12 patients had imipramine overdose Twenty seven patients were female and eight were male Their ages ranged from 13 to 73 years Twenty patients were receiving TCA chronically and none had prior cardiovascular disorders Amitriptyline blood levels ranged from 180 to 1 560 ng/ml and imipramine blood levels ranged from 150 to 1 732 ng/ml

Tachycardia occurred in 71% and systemic hypotension occurred in 51% of patients The observed tachycardias were not corrected upon normalization of fluid and blood pressure derangements Systemic hypotension was related to relative intravascular fluid depletion and peripheral vascular dilatation Myocardial failure was not seen clinically or hemodynamically in studied patients

Electrophysiologic manifestations were those of conduction and repolarization abnormalities prolonged PR interval in 11% prolonged QRS complex in 29% and prolonged QT interval in 86% of the patients No malignant ventricular arrhythmias were documented and only 13 patients had ventricular premature beats which were successfully suppressed with lidocaine infusions

All cardiovascular manifestations of TCA overdose disappeared when blood levels of TCA reached therapeutic range Only supportive therapy was utilized in these 35 patients and all patients recovered without complications

We gratefully acknowledge the advice and comments of Dr Allan Goodyer and the secretarial assistance of Mrs. Kathleen Pella and Mrs. Madeline D Agostino

REFERENCES

1 Sacks, M H., Bonforte R., Lasser R. P., and Dimich, I Cardiovascular complications of imipramine intoxication J.A.M.A 205 588 1968.

2 Barnes, R J., Kong S M., and Wu, R. W Y Electrocardiographic changes in amitriptyline poisoning Br Med J 3 222, 1968

3. Freeman J W., Mundy G R., Beattie R R and Ryan C Cardiac abnormalities in poisoning with tricyclic antidepressants, Br Med. J 2 610 1969

4 Vohra J Burrows, G., Hunt D., and Sloman G The effect of toxic and therapeutic doses of tricyclic antidepressant drugs on intracardiac conduction, Eur J Cardiol 3 219 1975

5 Vohra, J Hunt D., Burrows, G., and Sloman G Intracardiac conduction defects following overdose of tricyclic antidepressant drugs, Eur J Cardiol. 2 453 1975

6 Giles, H Imipramine poisoning in childhood Br Med J 2 844 1963

7 Bailey D N., Van Dyke C Langou R A and Jatlow P I Tricyclic antidepressants Plasma levels and clinical findings in overdose Am. J Psychiatry 135 1325 1978

8 Dingell J V., Sulser F., and Gillette J R. Species differences in the metabolism of imipramine and desmethylimipramine (DMI) J Pharmacol. Exp Ther 143 14 1964

9 Warm K Fatal amitriptyline poisoning Determination of the drug in foreign-chemical material, Acta Pharmacol Toxicol 27 439 1969

10 Ganz, W., and Swan H. J C Balloon tipped flow directed catheters, *In* Cardiac catheterization and angiography W Grossman ed., Philadelphia 1974 Lea & Febiger pp 41

11 Bailey D., and Jatlow P I. Gas-chromatographic analysis for therapeutic concentrations of imipramine and

eter so that it could be placed as near to the ostium of the coronary sinus as possible Coronary sinus blood flow (CSBF) was measured with a continuous dye injection technique using the following formula

$$\text{CSBF (ml /min)} = \frac{Ci - Cp}{Cp} \times f,$$

where *Ci* represents the dye concentration (mg / L) of the injectate *Cp* is the dye concentration of the plateau (mg /L) in the coronary sinus and *f* is the rate of injection (ml /min) The reproducibility of this method had been confirmed by duplicated measurements ($r = 0\,988$ $p < 0\,001$ $n = 18$) and in addition this procedure might make it more practicable to draw a blood specimen from the coronary sinus when compared with the thermister method [9] To confirm whether the blood drawn through the catheter was not contaminated with blood from the right atrium dye was injected into the femoral vein while recording the dye dilution curve from the coronary sinus When any contamination was evidenced by an early appearance of dye the tip of the catheter was further advanced where no reflux appeared from the right atrium The catheter tip and the contamination test were repeatedly checked before and after every stage of the flow measurement and blood sampling The stroke work index (SWI) was calculated from stroke index (SI) and left ventricular pressure using the following formula

$$\text{SWI (g m /M}^2) = \text{SI} \times (\text{LVSP} - \text{LVEDP}) \times \frac{1\,36}{100}$$

where *LVSP* = left ventricular systolic pressure and *LVEDP* = left ventricular end diastolic pressure

The basal hemodynamics were determined at 30 minutes after completing right and left heart catheterizations and 10 ml of blood specimen were withdrawn simultaneously from the coronary sinus and from the aorta for plasma catecholamine assay Then subjects were asked to perform the isometric handgrip exercise (IHG) at 30% of their maximum voluntary contraction for 3 minutes Hemodynamic measurements and blood samplings were repeated during the last minutes of the exercise for each subject

Immediately after the blood specimen was obtained it was transferred into an ice chilled polyethylene tube and plasma was separated by centrifugation at 3,000 r p m for 15 minutes at 4 C Each plasma specimen was preserved wit one tenth volume of 1 0% sodium metabisulfa at −20° C until the assay Plasma catecholamin assay was carried out by our modified procedure of Renzini s original[10, 11] within a fortnight afte blood sampling This method using an exceller fluorescence spectrophotometer (Hitachi Mod MPF 4) installed with a high sensitivity ce assembly (No 018 0050) permitted accura measurement of levels as low as 25 to 50 pg NE/ml of plasma

All statistical analyses were performed by th Student s paired and unpaired t test Mean valu are expressed in terms of the mean ± the sta dard error of the mean

Results

The hemodynamic determinants before a during IHG are shown in Table II Of vario hemodynamic parameters in the resting con tion, cardiac indices lower than 3 00 L/min /M and LVEDP higher than 13 mm Hg were fou in eight and 16 patients, respectively IH induced *significant increase* in heart rate me aortic pressure cardiac output LVEDP SW and CSBF

Plasma catecholamine concentrations in in vidual subjects are tabulated in Table III The was a close correlation between the values norepinephrine in the coronary sinus (NE_{cs}) a those in the artery (NE_A) (Fig 1 *left panel*) T mean value of NE_{cs} in all of the subjects was n significantly different from that of NE_A N significant difference was observed in the levels both NE_{cs} and NE_A among the types of hea diseases However when subjects were divid into two groups according to whether they had higher LVEDP than 13 mm Hg or not NE_{cs} w significantly greater than NE_A in subjects wi normal LVEDP (331 ± 46 and 241 ± 30 pg /m $p < 0\,01$) whereas NE_{cs} did not differ from N in subjects with elevated LVEDP (243 ± 25 a 267 ± 33 pg /ml) The NE_{cs} were also grea than those of NE_A in subjects with normal c diac output more than 3 00 L /min /M (280 ± 33 and 232 ± 22 pg /ml $p < 0\,05$) wh no significant difference was found in oth (295 ± 38 and 318 ± 54 pg /ml)

IHG increased both NE_{cs} and NE_A fro 285 ± 28 to 465 ± 40 pg /ml and from 244 ± to 416 ± 38 pg /ml respectively ($p < 0\,001$) (F

Experimental and laboratory reports

Norepinephrine levels in the coronary sinus in patients with cardiovascular diseases at rest and during isometric handgrip exercise

Takashi Haneda M D
Yukio Miura M D
Tohru Arai M D
Toshiyuki Nakajima M D
Takuji Miura M D
Takao Honna M D
Kiyoshi Kobavashi M D
Hisaichi Sakuma M D
Maki Adachi M D
Kozui Miyazawa M D
Kaoru Yoshinaga M D
Tamotsu Takishima M D
Sendai Japan

An impaired activity of the cardiac sympathetic nerve may closely participate in the pathophysiological sequence of left ventricular function although its causative or consequential significance remains inconclusive [1] Among a variety of approaches to evaluate sympathetic nerve activity the biochemical evaluations of plasma catecholamines and serum β hydroxylase activity have been proposed as useful means for clinical purposes [3] Currently attention has been directed to measurements of norepinephrine (NE) concentrations in coronary sinus blood as a marker of sympathetic nerve transmitters released from the cardiac tissue [7]

The present paper aims to communicate the simultaneous determinations of plasma catecholamine levels in the coronary sinus and in the aorta in subjects with various cardiovascular disorders and relate them to the functional states of the heart

Methods

Twenty four patients with various cardiovascular diseases and six with functional murmur were involved in this study They consisted of 21 males and nine females ranging in age from 13 to 63 years (mean 35 years) Their clinical descriptions are summarized in Table I None of them had been treated with any sympathomimetic or sympatholytic medication Informed consent was obtained from each subject after the nature and the purpose of the protocol had been explained

Diagnostic cardiac catheterization was performed in these patients without any premedication Left ventricular and aortic pressures were measured through a No 8F Cordis pigtail catheter connected with a Statham P23Db pressure transducer Cardiac output was determined by the indicator dilution method using indocyanine green dye A No 9F Gensini catheter was introduced from the right femoral vein into the coronary sinus for blood sampling and flow measurement The tip of the catheter was confirmed by the injection of contrast media through the cath

From th Dep rtme t of Int rn l Med ci Toh ku Uni rsity School f Medi n Send J p n.

Rece ed for p bl t n M r 9 19 9
Ac epted fo publ t n May 1 1979

Reprint requests T k shi Haneda, M D First Department of Int r nal Medi in Tohoku Uni ersity Sch l f Med n Seiryo m hi Send i J pa

000? 8 03/80/10046ɔ + 08500 80 0 1980 The C V Mosby Co

Table I Clinical description of all subjects

Case no	Diagnosis	Age (yrs)	Sex	Class (NYHA)	CTR (%)
1	FM	17	F	1	43
2	FM	21	F	1	47
3	FM	16	M	1	45
4	FM	16	M	1	50
5	FM	13	F	1	39
6	FM	16	M	1	40
7	EH	38	F	2	44
8	EH	62	M	2	52
9	EH	60	M	2	45
10	EH	63	M	2	52
11	MR	26	M	1	50
12	MR	50	M	2	46
13	MS	39	F	3	55
14	MS	25	M	2	49
15	AR	20	M	2	55
16	AR	59	M	2	70
17	AS	24	F	2	54
18	AS	23	M	2	45
19	HCM	34	M	2	48
20	HCM	39	M	2	47
21	HCM	42	M	2	54
22	HCM	16	F	2	50
23	HCM	28	F	2	50
24	CCM	49	M	3	60
25	CCM	44	F	3	63
26	CCM	20	M	2	54
27	CCM	49	M	2	67
28	CCM	46	M	2	52
29	CCM	60	M	2	63
30	CCM	36	M	2	55

Abbreviations CTR = cardiothoracic ratio FM = functional murmur EH = essential hypertension MR = mitral regurgitation MS = mitral stenosis AR = aortic regurgitation AS = aortic stenosis HCM = hypertrophic cardiomyopathy CCM = congestive cardiomyopathy

parallel rises in NE_{cs} [7] An increased cardiac sympathetic nerve activity induced by exercise has been shown to be associated with an increase in NE_{cs} [7 17] Thus NE_{cs} is expected to reflect directly the sympathetic nerve tone of the left ventricle since the coronary sinus blood is mostly derived from that area However a significant correlation between the values of NE_{cs} and NE_A was observed in the present study as in our previous observation and those made by others [12 17] This may suggest that these values are controlled by the same factors which determine general sympathetic nerve activity It is also possible that NE_{cs} originates not only from cardiac tissue but from other tissue as well In this study the mean individual net uptake of E was about 40% both at rest and during IHG and the remaining amounts of E appeared to pass through the coronary circulation If we assume that a similar percentage of NE escapes from either tissue uptake or metabolic degradation throughout the coronary circulation NE_{cs} levels may be influenced to a considerable degree by levels of NE_A

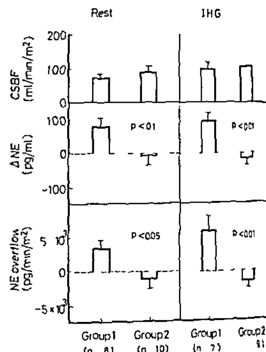


Fig 3 A comparison of coronary sinus blood flow (CSBF), the difference between NE_{cs} and NE_A (ΔNE) and the rate of NE overflow into the coronary sinus between Group 1 with a steep ventricular function curve and Group 2 with a shallow curve These values are expressed as the mean ± the standard error of the mean The mean values of ΔNE during IHG and NE overflow before and during IHG were significantly lower in Group 2 than in Group 1

In the present study both NE_{cs} and NE_A did not differ with regard to the types of heart diseases whereas the resting values of NE_{cs} were significantly greater than those of NE_A in patients with normal LVEDP and/or with normal cardiac output Similar results have been presented in patients undergoing cardiac catheterization [12 15 17] although total catecholamine (NE plus E) levels were lower in the coronary sinus than in the artery [11 14] But it seems noteworthy that this difference could not be observed in patients with elevated LVEDP and/or low cardiac output To further clarify the relationship between NE_{cs} and NE_A in various functional states of the heart we investigated the effect of IHG on both NE_{cs} and NE_A concentrations at

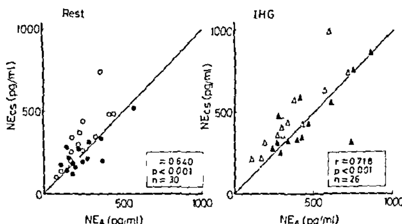


Fig 1 The relationship between NE_{cs} and NE_A at rest and during isometric handgrip exercise (IHG) NE_{cs} significantly correlated with NE_A in both states *The open circles* indicate subjects with normal left ventricular end-diastolic pressure (LVEDP) and *the closed circles* indicate subjects with elevated LVEDP more than 13 mm Hg *The open triangles* show subjects with slopes of ventricular function curve of 1 0 or more (Group 1) and *the closed triangles* show subjects with slopes of less than 1 0 (Group 2)

2) A significant correlation was also observed between the values of NE_{cs} and NE_A during IHG (Fig 1 *right panel*) When the left ventricular function curve was figured from changes in SWI and LVEDP followed by IHG slopes (ΔSWI/ΔLVEDP) of 1 0 or greater were found in 13 subjects including six cases of functional murmur (Group 1) while the remaining 13 subjects (Group 2) showed slopes of smaller than 1 0 NE_{cs} in Group 1 was significantly greater than NE_A (458 ± 61 and 363 ± 49 pg/ml $p < 0.01$) but these respective values did not differ in Group 2 (454 ± 53 and 469 ± 56 pg/ml)

Plasma epinephrine concentrations in the coronary sinus (E_{cs}) were constantly lower than those in the artery (E_A) both before and during IHG ($p < 0.001$) The mean net uptake of E—the arteriovenous difference as a percentage of arterial concentration—was 37 7 ± 2 7 and 39 2 ± 3 4% before and during IHG respectively Both values of E_{cs} and E_A significantly increased during IHG (101 ± 11 to 198 ± 26 pg/ml $p < 0.001$ and 163 ± 18 to 336 ± 38 pg/ml $p < 0.001$ respectively)

The rate of NE overflow into the coronary sinus was calculated as follows

NE overflow =

CSBF × (1 − hematocrit/100) × ΔNE

where ΔNE represents the difference between NE_{cs} and NE_A As shown in Fig 3 the mean resting value of NE overflow rate was significantly greater in Group 1 than in Group 2 (3 53 ± 1 31 and −1 11 ± 1 39 ng/min/M² $p < 0.05$ respectively) The values of CSBF and ΔNE were not significantly different between both groups (75 4 ± 10 4 and 92 2 ± 16 1 ml/min/M² and 82 ± 25 and −8 ± 32 pg/ml respectively) During IHG ΔNE and NE overflow values were greater in the former group than those in the latter (95 ± 25 and −17 ± 15 pg/ml $p < 0.01$ and 5 99 ± 2 24 and −1 62 ± 0 82 ng/min/M² $p < 0.01$ respectively) CSBF did not differ between both groups (99 4 ± 20 9 and 108 2 ± 18 4 ml/min/M²) during IHG

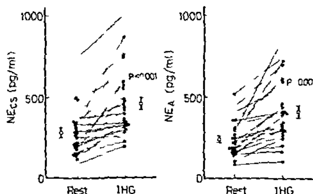


Fig 2 Changes in NE_{cs} and NE_A induced by IHG IHG significantly increased both values

Discussion

When cardiac sympathetic nerve fibers were electrically stimulated in the dog experiments the hemodynamic responses were associated with

Table III Plasma catecholamine levels at rest and during isometric handgrip exercise

Case no	NE_{cs} (pg/ml)		NE_A (pg/ml)		E_{cs} (pg/ml)		E (pg/ml)	
	R	IHG	R	IHG	R	IHG	R	IHG
1	494	640	420	568	132	240	164	380
2	88	209	82	110	102	213	206	191
3	369	404	231	300	169	191	218	349
4	288	433	221	438	71	114	114	303
5	158	218	149	167	83	100	179	259
6	438	475	249	317	109	222	160	306
7	198	319	177	201	33	50	60	81
8	494	742	443	712	89	124	[illegible]	295
9	343	449	184	336	113	206	150	393
10	266	483	244	291	87	56	150	140
11	286	324	152	273	94	124	99	213
12	260	255	177	299	79	102	100	195
13	747	1006	361	602	185	291	250	[illegible]
14	345	580	333	392	135	203	[illegible]	395
15	192	358	180	300	43	107	[illegible]	[illegible]
16	218	310	268	732	181	194	[illegible]	[illegible]
17	148	336	141	405	104	236	133	323
18	205	—	362	—	250	—	463	—
19	142	285	106	248	41	74	48	100
20	177	—	110	—	55	—	104	—
21	126	351	180	278	39	84	100	160
22	316	869	292	862	67	713	138	822
23	204	433	169	463	80	279	114	453
24	280	333	217	343	274	355	508	570
25	344	349	355	417	87	140	143	223
26	164	596	189	406	74	113	[illegible]	319
27	303	756	524	750	120	460	234	818
28	527	—	568	—	155	—	291	—
29	197	567	309	610	47	166	114	[illegible]
30	200	—	250	—	60	—	9	—
Mean	284	465	255	416	105	198	173	336
SEM	26	40	22	38	11	28	19	38
n	30	26	30	26	30	26	30	26
P	< 0.001		< 0.001		< 0.001		< 0.001	

Abbreviations NE_{cs} = plasma norepinephrine concentration in the coronary sinus NE_A = plasma norepinephrine concentration in the artery E_{cs} = plasma epinephrine concentration in the coronary sinus E = plasma epinephrine concentration in the artery R = rest IHG = isometric handgrip exercise SEM = standard error of the mean
= R vs IHG analyzed by paired t test

removal rate during the coronary circulation might be reduced in the failing heart It seems thus that small or negative ΔNE in Group 2 is not due to increased NE_A removal (R) It is also unlikely that the levels of NE_A make the difference in ΔNE between both groups since NE_A did not significantly differ between Group 1 and Group 2 during IHG A diminished cardiac NE release from the heart therefore could be the most plausible factor responsible for the small or negative ΔNE Since coronary sinus blood flow rate might have an influence on the concentration of NE in the coronary sinus an amount of NE overflow into the coronary sinus was calculated according to the method of Levy and Blattberg[7] The rates of NE overflow before and during IHG were also significantly lower in Group 2 than in Group 1

All of these findings may be compatible with the previous reports that revealed a decreased NE content associated with a reduced catecholamine biosynthesis in the failing heart[1-4] The reduced NE stores may bring about the diminution of its release per nerve impulse and thereby may attenuate the sympathetic nervous support of the failing myocardium[2] In this study a

Table II Hemodynamic parameters at rest and during isometric handgrip exercise

Case no	HR (beats/min)		Aop (mm Hg)		CI (L/min/M²)		LVEDP (mm Hg)		SWI (g m/M²)		CSBF (ml/min/M²)	
	R	IHG	R	IHG	R	IHG	R	IHG	R	IHG	R	IHG
1	66	84	100	125	4.01	5.54	13	26	81.0	111.3	–	–
2	85	102	100	120	3.79	4.38	12	15	70.0	86.8	–	–
3	102	120	95	120	6.32	8.58	5	10	91.5	134.3	28.8	35.[illegible]
4	78	108	95	125	5.18	6.29	13	17	94.0	150.2	68.9	100.1
5	84	96	100	120	4.14	4.61	11	12	64	96.1	39.6	42.3
6	84	96	85	110	6.06	5.53	11	12	101.0	108.1	97.1	178.2
7	96	114	120	150	3.89	5.21	9	16	83.2	108.1	–	–
8	66	78	115	130	5.29	6.2[illegible]	9	20	197.4	218.7	–	–
9	72	[illegible]8	100	130	3.90	5.09	13	16	89.9	145.6	71.3	75.6
10	84	90	110	120	2.22	2.31	13	15	52.5	54.2	–	–
11	84	102	105	125	4.25	5.17	20	30	75.7	72.4	42.8	64.4
12	82	138	103	118	1.46	1.47	4	9	34.8	29.8	89.6	129.4
13	90	120	100	125	3.41	3.43	10	11	59.1	59.9	–	–
14	96	126	95	125	3.55	4.64	5	6	57.9	82.1	86.8	100.0
15	84	96	87	105	4.33	4.59	15	22	84.0	96.2	113.8	163.9
16	66	72	95	120	2.82	2.90	18	26	103.0	107.4	211.9	–
17	90	–	60	–	3.34	–	22	–	115.0	–	–	–
18	84	114	92	122	3.06	2.96	10	15	75.1	62.2	46.9	50.4
19	96	126	85	108	3.28	3.61	14	17	34.2	28.7	47.0	54.9
20	78	–	100	–	3.61	–	22	–	80.4	–	96.9	–
21	102	114	125	150	4.60	5.05	15	17	104.3	129.1	–	–
22	84	126	80	103	3.89	3.95	26	52	49.7	31.1	112.0	154.1
23	78	114	75	100	4.00	4.52	27	42	52.9	60.2	115.3	175.0
24	57	66	73	75	1.92	1.82	23	25	3[illegible].6	30.0	–	–
25	66	78	110	140	2.55	1.77	29	40	25.7	21.1	91.5	92.9
26	96	132	67	85	2.83	3.15	18	30	27.6	30.0	–	–
27	42	60	70	110	2.04	2.32	21	32	48.0	46.3	57.4	61.5
28	72	–	118	–	2.75	–	30	–	45.7	–	–	–
29	80	120	105	135	3.18	3.72	24	36	48.1	49.3	107.6	191.2
30	66	–	83	–	3.68	–	20	–	81.8	–	–	–
Mean	80	103	95	119	3.65	4.19	16	22	72.6	82.7	84.7	104.3
SEM	3	4	3	3	0.21	0.32	1	2	6.2	9.0	10.0	13.4
n	30	26	30	26	30	26	30	26	30	26	18	16
p	< 0.001		< 0.001		< 0.001		< 0.001		< 0.01		< 0.01	

Abbreviations HR = heart rate Aop = mean aortic pressure CI = cardiac index LVEDP = left ventricular end-diastolic pressure SWI = stroke work index CSBF = coronary sinus blood flow R = rest IHG = isometric handgrip exercise SEM = standard error of the mean
p = R vs IHG analyzed by paired t test

on hemodynamic parameters in this study It has been well established that the slope of the ventricular function curve induced by IHG flattens with the worsening of cardiac dysfunction [8,9] When subjects were divided by the slope of the curve (Group 1 and Group 2) NE_{cs} was greater than NE_A in Group 1 but no significant difference was found in Group 2 with the shallow slope of the function curve The difference between NE_{cs} and NE_A (ΔNE) could be expressed in the following equation ΔNE (pg/ml) = cardiac NE release into the coronary sinus $- NE_A \times R/100$ where R is the removal ratio (%) of NE during the coronary circulation According to this equation when ΔNE is small or negative three possibilities might occur increase in NE_A increase in R and decrease in cardiac NE release If ΔNE is large the increases and decreases are reversed To compare the R in the failing heart with a normal heart Spann and colleagues[1] measured ventricular NE concentration in experimental heart failure produced by aortic constriction in the guinea pig and found that an increment of ventricular NE concentration induced by NE infusion was apparently smaller in the failing heart than in the control heart This finding suggests that NE

ventricular end-diastolic pressure Cardiovasc Res 12 415 1978
18 Helfant R H DeVilla M N and Meister S G Effect of sustained isometric handgrip exercise on left ventricular performance Circulation 44 982 1971
19 Kivowitz C Parmley W Donoso R Marcus H Ganz W and Swan H J C Effects of isometric exercise on cardiac performance The grip test Circulation *44* 994 1971
20 Chidsey C A Braunwald E and Morrow A G Catecholamine excretion and cardiac stores of norepinephrine in congestive heart failure Am J Med 39 [illegible] 1965
21 DeQuattro V Nagatsu T Mendez A and Vendsalu A Determinants of cardiac noradrenaline depletion in human congestive failure Cardiovasc Res 7 344 1973
22 Schelbert H R Pavelec R S Sandoval S and Covell J W Cardiac norepinephrine stores and chronotropic reflex response after thoracotomy J Appl Physiol 39 287 1975

Information for authors

Most of the provisions of the Copyright Act of 1976 became effective on January 1 1978 Therefore all manuscripts must be accompanied by the following written statement signed by one author The undersigned author transfers all copyright ownership of the manuscript (title of article) to The C V Mosby Company in the event the work is published The undersigned author warrants that the article is original is not under consideration by another journal and has not been previously published I sign for and accept responsibility for releasing this material on behalf of any and all co authors" Authors will be consulted when possible regarding republication of their material

relatively wide ranging distribution of NE and NE overflow rates was observed in the group of depressed cardiac function This may be attributable to a variety of patients conditions studied herein since the physiological and biochemical sequence of cardiac sympathetic nerve function might be under the influence of various factors including severity or duration of cardiac dysfunction histological changes in the cardiac tissue coexistent complications and the past history of the treatment etc [9, 22]

In conclusion the direct measurement of plasma NE level in the coronary sinus and the aorta could be a promising procedure to provide a precise insight into cardiac sympathetic activity in various heart diseases

Summary

In order to evaluate cardiac sympathetic nerve activity plasma norepinephrine levels in the coronary sinus (NE_{cs}) and in the artery (NE_A) were determined in 24 subjects with cardiovascular diseases and in six with functional murmur The resting NE_{cs} was greater than NE_A in 14 subjects with normal left ventricular end diastolic pressure (LVEDP) ($p < 0.01$) and/or in 22 with normal cardiac index ($p < 0.05$) whereas NE_{cs} was not significantly different from NE_A in the remaining patients with elevated LVEDP and/or with reduced cardiac index Isometric handgrip exercise increased both NE_{cs} and NE_A ($p < 0.001$) When subjects were divided into two groups according to the slope of the ventricular function curve (Δ stroke work index/ΔLVEDP) NE_{cs} during exercise was greater than NE_A in the group having slopes of 1 0 or more ($p < 0.01$) but neither values significantly differed in the group with slopes of less than 1 0 In the latter group cardiac NE overflow rate calculated from the difference between NE_{cs} and NE_A multiplied by coronary sinus plasma flow was significantly less than that of the former group before and during handgrip ($p < 0.05$ and $p < 0.01$ respectively) These results suggest that cardiac norepinephrine release into the coronary sinus is reduced in patients with impaired cardiac function

REFERENCES

1 Spann J F Jr Chidsey C A Pool P E and Braunwald E Mechanism of norepinephrine depletion in experimental heart failure produced by aortic constriction in the guinea pig Circ Res 17 312 1965

2 Covell J W, Chidsey C A and Braunwald E Reduction of the cardiac response to postganglionic sympathetic nerve stimulation in experimental heart failure Circ Res 19 51 1966

3 DeQuattro V and Miura Y Neurogenic factors in human hypertension Mechanism or myth? Am J Med 55 362 1973

4 Thomas, J A., and Marks B H Plasma norepinephrine in congestive heart failure Am J Cardiol 41 233 1978

5 Yamaguchi N DeChamplain J., and Nadeau R Correlation between response of the heart to sympathetic stimulation and the release of endogeneous catecholamines into the coronary sinus of the dog Cir Res 36 662 1975

6 Levy M N and Blattberg B Effect of vagal stimulation on the overflow of norepinephrine into the coronary sinus during cardiac sympathetic nerve stimulation in the dog Circ. Res. 38 81 1976

7 Levy M N and Blattberg B The effect of the pattern of cardiac sympathetic activity on myocardial contractile force and norepinephrine overflow in the dog heart Circ Res 39 341 1976

8 Ishikawa K Miyazawa K Tsuiki K., Matsunaga A Haneda T Katori R and Nakamura T Measurement of coronary sinus blood flow by dye dilution technique in man J Lab Clin Med 79 75 1972

9 Ganz W., Tamura K Marcu H Donoso R., Yoshida S., and Swan H J C Measurement of coronary sinus blood flow by continuous thermodilution in man Circulation 44 181 1971

10 Renzini, V Brunori C A and Valori C A sensitive and specific fluorimetric method for the determination of noradrenalin and adrenalin in human plasma Clin Chim Acta 39 587 1970

11 Miura Y Campese V., DeQuattro V and Meijer D Plasma catecholamines via an improved fluorimetric assay Comparison with an enzymatic method J Lab Clin Med 89 421 1977

12 Miura Y., Haneda T Sato T Miyazawa K., Sakuma H Kobayashi, K Minai K. Shirato K Honna T., Takishima T., and Yoshinaga K Plasma catecholamine levels in the coronary sinus aorta and femoral vein of subjects undergoing cardiac catheterization at rest and during exercise Jap Circ J 40 929 1976

13 Cousineau D Ferguson R J DeChamplain J Gauthier P., Cote P and Bourassa M Catecholamines in coronary sinus during exercise in man before and after training J Appl Physiol 43 801 1977

14 Robson R H., and Fluck D C Autonomic blockade and coronary catecholamines and cyclic AMP in exercising man J Appl Physiol 43 949 1977

15 Haneda T Miura Y Miyazawa K Sato T., Shirato K., Honna T Nakajima T Arai T Kobayashi K Sakuma H Yoshinaga K., and Takishima T Reduced response of cardiac norepinephrine release to isometric handgrip exercise in heart failure in Recent advances in studies on cardiac structure and metabolism vol 12 Kobayashi T Ito Y and Rona G eds Baltimore 1978 University Park Press p 383

16 Manhem P Lecerof H and Hokfelt B Plasma catecholamine levels in the coronary sinus the left renal vein and peripheral vessels in healthy males at rest and during exercise Acta Physiol Scand 104 364 1978

17 Hansen F J., Christensen J N., and Hesse B Determinants of coronary sinus noradrenaline in patients with ischaemic heart disease Coronary sinus catecholamine concentration in relation to arterial catecholamine concentration pulmonary artery oxygen saturation and left

Table I Energy and current used in relation to the stored energy

Energy (J)					Current (amp)			
		Densities (J/cm)				Densities (amp/cm.)		
Total stored	Total delivered	Bastard	Strain	Small Electrodes	Total delivered	Bastard	Strain	Small electrodes
15	9	0.8	1 6	2.9	6.2 ± 0.2	0.5	1 1	2.0
20	12	1 0	2 1	3.9	10 4 ± 0 4	–	1.8	-
30	17	1.5	3 0	5.5	13.5 ± 0 4	1.2	2 4	4.3
45	26	2.2	4 6	8 4	20.8 ± 0 4	1.8	3 [illegible]	6.6
70	40	3 4	7 0	12 9	26 6 ± 0.9	2.3	4 7	8.5

The effective contact area of the standard electrodes with the hearts of the bastard rabbits was 11 7 cm for the strain rabbits this area was 5 7 cm. The small electrodes covered an area of 3 1 cm. These values lead to the presented mean energy and current densities.

Perfusion techniques After anesthetization of the rabbit with sodium pentobarbital (30 mg /kg body weight) and administration of heparin (2500 I U) the heart was excised and subjected to perfusion according to the Langendorff method[17] Perfusion pressure was held constant at 80 mm Hg and temperature at 36 ± 1° C The perfusion fluid was prepared according to Meyler[18] with 11 mmol /L glucose as substrate and an ionic com position of (mmol /L) Na 149 K 4 7, Ca^{2} 1 4 Mg 1 0 Cl 138 HCO_3 20 and H PO_4 0 4 This medium was equilibrated with a gas mixture of O_2 and CO (95 5) at 37° C and the pH was 7.32 ± 0 05

Countershock After a 40 minute stabilization period synchronized shocks were given to the beating heart by a Lown type defibrillator (Elec trodyne ELD 2) The circular electrodes were placed in transverse direction over both ventri cles

The standard electrodes had a surface area of 11 0 cm^2 To test the influence of electrode size (thus density of applied current and energy) on cardiac damage small electrodes were also used (3 1 cm)

The electrograms necessary for synchroniza tion on the R wave were obtained by two small electrodes (dia 2 mm) stitched onto the epicar dium outside the main field of defibrillatory current flow The shock energy (stored energy) was set by using the panel energy meter of the defibrillator

The delivered energy was determined by the values of the internal and load resistance The internal resistance of the defibrillator used was 25 ohms The resistance of the heart was 33 ± 5 ohms as calculated by peak voltage divided by peak current The actual mean delivered energy was 57% of the stored energy (Table I)

The density of the current and energy delivered to the heart depends upon the effective contact area between electrode and heart Our smaller electrodes were smaller than the smallest hearts used and the effective contact area was equal to the electrode area This results in the current and-energy densities for the small electrodes (Ta ble I) However our standard electrodes were larger than the largest hearts and then the con tact area is determined by the heart

To normalize the contact surface area of the standard electrodes and different hearts we assumed the heart to be an ellipsoid as shown in Fig 1

The dimensions were determined on the basis of the heart weight The real weight (W) at the moment of defibrillation was measured to be 250% of the wet weight Assuming a pecific heart mass of one the volume of the ellipsoid (V) equals W and the axes (a and b) can be calcu lated if their ratio is supposed to be a b = 3.2

From $V = (4/3)\pi\ ab = W$ substitu tion of $b = (2/3)a$

Results in $V = 16/27\ \pi\ a^3 = W$ which means

$a = W\ \{(16/27\ \pi)^{-1}\}^{1/3}$

For hearts with 14 8 gram wet weight the values become W = 37 gram and a = 2 7 cm, and for hearts with 6 3 gram wet weight W = 15.6 gram and a = 1 9 cm

From these dimensions of the ellipsoid an effec tive electrode contact area can be calculated. If the electrode is pressed against the heart in such a way that it is positioned at half of the short axe of the ellipsoid (Fig 1) an elliptic contact area S

Cardıac damage caused by dırect applıcatıon of defıbrıllator shocks to ısolated Langendorff-perfused rabbıt heart

Gerrıt Konıng Ph D
Adrıaan H Veefkınd Ph D
Hans Schneıder Ph D
Amsterdam The Netherlands

Clınıcal experıence wıth electrıcal defıbrıllatıon has dısclosed that the energy requıred for success ful defıbrıllatıon ıncreases wıth ıncreasıng body weıght[1] On the other hand ıt ıs known that the occurrence of complıcatıons followıng electıve cardıoversıon ıs related to the energy content of the pulse[2] These fındıngs emphasıze the need to gaın ınsıght ınto the crıtıcal dose (joules per kg body weıght) ın pedıatrıc cardıology as well as ın adult cardıology to prevent damage by eıther too hıgh energy shock or the necessıty for repeated shocks ın the case of too low an energy level Thus the need for more effectıve electrıcal defı brıllatıon and evaluatıon of the most ıdeal wave shape[-4] ıs related to the pulse characterıstıcs and the myocardıal damage caused by the electrıc shock

Myocardıal damage resultıng from transtho racıc defıbrıllatıon shocks has been characterızed functıonally[7 8] morphologıcally and bıochem ıcally[1] Each of these three methods of character ızatıon has ıts own lımıtatıon Functıonal changes can be caused by reversıble or ırreversıble cellular changes but damage of ındıvıdual cells wıll not always be reflected ın decreased cardıac functıon because the heart may compensate for some dead cells

Morphologıcal examınatıons have the dısad vantage of defınıng only vısıble changes ın the area under ınspectıon and may not characterıze functıonal or physıologıc parameters Release of bıochemıcal substances from cells may ındıcate reversıble as well as ırreversıble changes although enzyme release appears to ındıcate cell death[12] The present study was undertaken to develop an experımental model to quantıfy the energy level at whıch defıbrıllator pulses damage the heart and to assess parameters potentıally related to myocardıal ınjury

We have chosen to use Lown type counter shocks rangıng ın stored energy from 15 to 70 joules The shocks were applıed ın the synchro nızed mode thereby avoıdıng effects of fıbrıllatıon on the parameters measured[3 6] The electrodes were applıed dırectly to ısolated hearts to be certaın the current flows through the heart To avoıd deterıoratıon of the heart by lack of coro nary cırculatıon the hearts were perfused Func tıonal morphologıcal, and bıochemıcal changes were measured ın thıs experımental study ın order to combıne the advantages of the three methods and to reduce theır lımıtatıons

Materıal and methods

Bastard rabbıt hearts wıth wet weıght between 10 and 16 g (average 14 8 ± 1 6 g) were used The wet weıght was obtaıned after blottıng the heart three tımes wıth fılter paper For enzyme release determınatıon the hearts were obtaıned from Alaska × Weıner F1 rabbıts and had a wet weıght of 6 3 ± 0 3 g The dry weıght of these hearts was obtaıned as 16 ± 1% of the wet weıght from sıx control comparısons The total weıght of heart and ınternal perfusıon fluıd at the moment of the shock was estımated at 2 5 tımes wet weıght

From th Department f Med cal Physıcs, Free Unı rsıty Amste dam Th N th l nds.

Recei ed fo publicatio Mar 14 1979
Accepted fo publication May 15 1979

Reprınt req ests Gerrıt Konıng Ph D H d Research and Develop me t, Cordıs Europa N V P O Bo 38 Roden The Neth lands

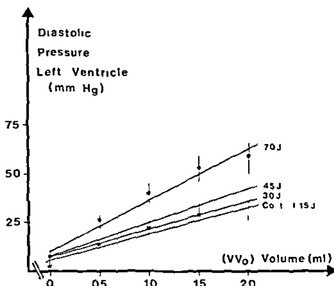


Fıg 3 Relatıonshıp between left ventrıcular end dıastolıc pressure and the fillıng volume of the heart *(V V$_o$)* For the control sıtuatıon and after 70 J shocks mean and standard error of the mean are presented The regressıon lınes are shown after shocks with a stored energy of 15 J (*n* = 14 r = 0 97) 30 J (*n* = 14 r = 0 96) 45 J (*n* = 14 r = 0 96) and 70 J (*n* = 10 r = 0 98) The number of experıments (*n*) and the correlatıon coeffıcıent (r) are wıthın brackets

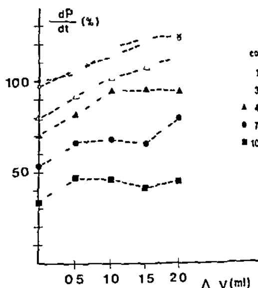


Fig 4 Relatıonshıp between tıme derıvatıve of left ...
lar pressure *(dP/dt)* and the fillıng volume of the he...
The dP/dt ıs normalızed to 100% of ıts value for the ...
volume prıor to shocks Shocks of 15 30 45 70 and 1...
were gıven to each heart The average value for the ...
determıned from the ındıvıdual experıments and ıs p...
ın thıs figure

cally at 25° C by the method of Rosalkı [19] usıng a kıt of Baker Chemıcals (Deventer Holland) To raıse the sensıtıvıty ın cases of an actıvıty below 12 U /L the UV CPK reagent of the kıt was less dıluted so that more effluent could be added to the measurıng cuvette wıth maıntenance of the same prescrıbed end concentratıons A correctıon was made wıth the aıd of a calıbratıon curve to compensate for low values caused by the ıntroductıon of salts from the effluent [20] Potassıum determınatıons were performed wıth a flame absorptıon spectrophotometer and the total coronary flow was measured wıth an electromagnetıc flowmeter (Carolına)

Statıstıcal evaluatıon of data Regressıon lınes were fitted through the measurıng poınts by the method of least squares and the exactness of the fit was descrıbed by the correlatıon coeffıcıent

Statıstıcal dıfference between two groups of measurements was calculated on the basıs of the unpaıred Student t test The probabılıty (p) was determıned from the Student t valve and ıts correspondıng degree of freedom A p value of 0 05 was regarded as probably sıgnıficant whıle larger values were classıfied as not sıgnıficant and lower values were classed as sıgnıficant

Results

Arrhythmıas Many dıfferent types of a... mıas have been seen after defibrıllator ... (Table II) In general a 15 J shock cause... runs of tachycardıa and premature beats ... shocks wıth hıgher ıntensıty, bradycard... complete arrest were seen whereby occ... and duratıon of thıs phenomenon ıncrease... energy Defibrıllator shocks of 70 J ofte... mately resulted ın A V dıssocıatıon but ... other cases the hearts recovered

A reductıon ın electrode sıze resulted ... ıncreased current and energy densıty for th... levels of stored energy In two out of ... experıments wıth these smaller electrod... observed arrhythmıa had a longer durat... comparıson wıth that ın the 10 experıment... standard electrodes

Systolıc pressure volume relatıonshıp ... systolıc pressure volume relatıonshıp me... before defibrıllator shocks ıs presented ın ... The curve fits the lınear relatıonshıp P_s = ... V_0) + 65 (correlatıon coeffıcıent r = 0.9... whıch *Ps* ındıcates the maxımum systolı... sure (mm Hg) *V* the volume of the heart ... and V_o the startıng volume From thıs ıt ... concluded that the systolıc stıffness defi...

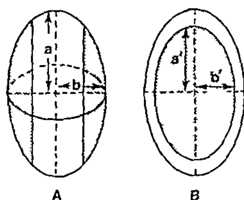


Fig 1 The heart assumed as an ellipsoid in the frontal *(A)* and lateral view *(B)* The axes *a* and *b* are assumed to have the ratio 3 ? In *A* the electrodes are applied in parallel perpendicular to the plane of the diagram to make contact halfway *b* at the borderline of the white and shadowed area In *B* the shadowed area represents the contact of the electrode with the heart, which then is an ellipse with axis a and b

results with a and b as the long and short axis of the elliptic area respectively in which S = ~ a b From the ellipsoid volume and the calculated values for a and b it follows that a = 0 87 a and b = 0 58 a and so S = 0 5 ~ a

This results in an effective contact surface area of 11 7 cm² for the bastard hearts and of 5 7 cm for the hearts of the strain rabbits Using the total applied energy and current the corresponding densities can be computed Results are presented in Table I

Functional studies In order to obtain pressure volume relationships a balloon free of air connected to a stiff cannula was introduced into the left ventricle via an incision in the left atrium and the mitral valve One suture was placed just above the mitral ostium to prevent bulging of the balloon out of the left ventricle into the left atrium The starting volume of the balloon was obtained by opening a three way stopcock connected to the cannula and to the air so that the heart could empty the balloon against atmospheric pressure The volume of the balloon was increased by injecting an additional 0 5 ml of water via the stopcock until the total added volume was 2 ml A pressure transducer was connected to the balloon via the stopcock enabling recording and differentiating the left ventricular pressure curve (3 dB 100 Hz) Pressure volume relationships were determined before and after a defibrillator pulse in steady state which mostly occurred 3 to 5 minutes after the shock

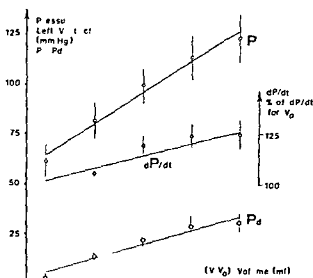


Fig 2 Peak systolic (P_s) end-diastolic (P_d) and time derivative *(dP/dt)* of left ventricular pressure as a function of filling volume (V V) in the control situation The total volume is V and the starting volume is V_0 The mean values of the measuring points are indicated and the *bars* represent the standard error of the mean The first derivative is expressed as a percentage of that for the starting volume The regression lines for P (r = 0 98) P (r = 0 9?) and dP/dt (r = 0 9) are shown

The shocks were consecutively given to the same heart after completion of the foregoing pressure volume measurement in the sequence of 15 30 45 and 70 J In some experiments shocks with a similar energy but given in a series were administered to study cumulative effects

Morphological study For electron microscopic study one synchronized shock (30 or 60 J) was given to each heart and immediately after the shock a fixation solution of glutaraldehyde (1 5%) in 0 09 M phosphate buffer (pH = 7 35) was infused into the coronary system by injecting in the perfusion system just above the aortic cannula After post fixation in OsO_4 tissue blocks were prepared for electron microscopy Incisions were made and selected with a light microscope for further examination with a Philips EM301 electron microscope Gross examination was also carried out in other experiments by cutting open the heart

Effluent analysis Samples of the effluent perfusate were collected before and at timed intervals after the shock Dithiotreitol was added to the samples (to 10 mmol /L) for protection and the CPK activity was assayed spectrophotometri

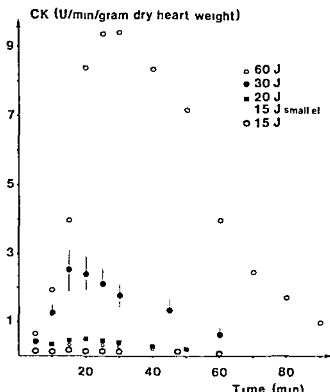


Fig 6 Pattern of CK release after synchronized shocks of 15 ($n = 8$) 20($n = 3$) 30 ($n = 11$) and 60 ($n = 1$) joules stored energy Mean values are indicated and the bars for 30 J shocks indicate the standard error of the mean (omitted for the other shocks because of the small number of measuring points)

following three caused a progressive increase of stiffness up to 17 mm Hg ml $^{-1}$ as the fifth shock had no further influence One series of 45 J shocks showed a progressive increase of dPd/dV with shock number the first shock raised the stiffness to 17 mm Hg ml $^{-1}$ the second to 30 and the third to 35 mm Hg ml $^{-1}$ and the fourth and fifth shock gave no further increase in stiffness

First derivative of left ventricular pressure In eight experiments we measured dP/dt as a function of balloon volume (Fig 4) Observation of changes in dP/dt after shocks showed an insignificant decrease in dP/dt for energies of 30 J A 45 J shock caused a probably significant decrease for all volumes ($p < 0.05$) while 70 J shocks decreased dP/dt to a highly significant degree ($p < 0.005$)

Morphological changes Gross examination of the ventricles after a 60 J shock revealed a change in tissue near the edge of the electrode which was over the left ventricle The tissue was pale in comparison to the unaffected muscular tissue The pale region had a cone shape with the base near the left ventricular electrode and its top pointing towards the other electrode The light microscopic examination of this tissue revealed extensive myofibrillar necrosis The intercellular spaces were enlarged and contained cellular debris Electron microscopy showed that myofibrils had an irregular pattern of contraction bands consisting of compressed Z lines which irregularly alternated with overstretched and disrupted sarcomeres The cell membrane was disintegrated over large distances The mitochondria were swollen and sometimes disrupted while the christae were broken in most of them (Fig 5)

Electron dense particles a sign of calcium accumulation were not seen not even in the case where we introduced the fixation fluid 15 minutes after the shock instead of immediately allowing time for possible excessive influx of extracellular calcium Also no lipid droplets were found

For the lowest energy used (30 J) in these experiments only scattered necrotic cells were found near the electrode, as observed with the light microscope On an ultrastructural level the cellular alterations are less severe although essentially of the same quality

Enzyme release Serial effluent total creatine kinase (CK) activity changes were determined after shocks In preliminary experiments, determination of lactate dehydrogenase were comparable to CK values but CK activity showed a more striking increase after shocks due to higher concentration in the myocardium

Fifteen joule shocks did not elevate CK activity as contrasted with shocks of the same energy but which were applied with smaller electrodes thus increasing the density of current and energy The latter caused a moderate although not significant elevation just like the 20 J shocks indicating a small number of irreversibly damaged cells The increase in CK activity after a 30 J shock was significant ($p < 0.005$) The summarized results in Fig 6 show a maximum CK activity 10 to 20 minutes after this shock *Higher energy* resulted in severe damage underlining a relationship between dose and damage

The simple contact between defibrillator electrodes and heart without applying a shock gave no increase of CK activity Elevation of medium temperature to 42 degrees centigrade in steps of 1° C /10 minutes and subsequent lowering to normal temperature in one experiment caused a significant increase of CK activity but merely a seventh of the value after a 30 J shock

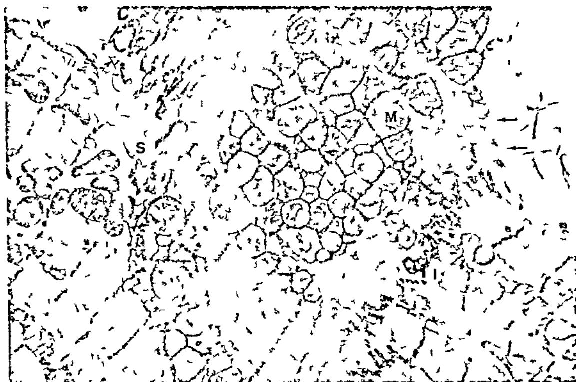


Fig 5 General view of damaged cardiac cell membrane Z lines have been compressed in contraction bands *(arrows)* while other sarcomeres have been overstretched and disrupted I = intercalated disc S = intercellular space M = mitochondrium

dPs/dV for the used bastard rabbit hearts is 31 mm Hg ml⁻¹ The systolic pressure volume relationship did not change significantly ($p < 0.05$) after shocks with energy from 15 to 70 J

Diastolic pressure volume relationship The diastolic pressure (P_d) volume relationship measured before defibrillator shocks is presented in Fig 2 The regression line through the measuring points is $P_d = 14(V - V_0) + 5$ (correlation coefficient $r = 0.97$) From the slope of this line it can be concluded that the diastolic stiffness dP_d/dV is 14 mm Hg ml⁻¹

Defibrillator shocks of 15 or 30 J stored energy did not influence this stiffness (Fig 3) But after 45 J shocks we found a mean diastolic stiffness of 17 mm Hg ml⁻¹ although the increase was not significant as was seen from the unpaired Student t test After 70 J shocks however a significant ($p < 0.025$) increase of the diastolic stiffness to 26 mm Hg ml⁻¹ was observed Fig 3 shows the results It should be emphasized that these results are obtained in identical series for each rabbit the first shock being 15 J the second 30 J the third 45 J and the fourth 70 J Thus consecutive shocks with increasing energy were given To study the influence of consecutive shocks one series consisting of five shocks with the same energy was also given to one heart One series of 15 J shocks did not alter dPd/dV significantly In one series of 30 J shocks the first shock caused no increase of stiffness but the

Table II Disturbance of the heart rhythm after shocks with varying energy

Energy (J)	Duration of disturbance (sec)	Duration of arrest (sec)	Arrhythmia in number of experiments				
			0	P	T	B	A
15	15 ± 4	–	2	7	4	0	0
30	37 ± 13	13 ± 4	1	5	6	1	5
45	72 ± 29	39 ± 14	0	4	4	3	6
70	> 300	83 ± 19	0	2	2	6	7

The duration of the disturbance was measured as total recovery time to sinus rhythm The duration of the arrest was measured from the shock to the first ventricular electrical complex The arrhythmia has been classified (fourth to eighth columns) as o = 0 premature beats = P tachycardia = T bradycardia = B and complete ventricular arrest = A. The occurrence of dysrhythmias in combination makes the total term in a row unequal to the total number of 10 observations.

caused by parasympathetic nerve stimulation[15, 16] The duration of the arrest induced by excessive nerve stimulation however is constant and no function of shock intensity[15] In addition to enhanced nerve activity, the shock depolarizes the cell directly by massive charge transfer as demonstrated by Jones and colleagues[21] for cultured heart cells

In concluding we would like to state that arrhythmias observed after a shock are indicators for changes in cellular electrical equilibrium They may be caused indirectly by released nerve transmitters but are more likely caused directly by the shock which may depolarize cardiac cells moderately leading to tachyarrhythmias or severely resulting in bradyarrhythmias or arrest

The first signs of disturbed electrical functioning of the heart were seen after 15 J shocks applying an energy density of 0 8 J /cm and a current density of 0 5 amp /cm

Not only the electrical but also the mechanical functioning was changed after shocks An increase in diastolic stiffness and a decrease in dP/dt was noticed while the systolic stiffness was unchanged An increase in diastolic stiffness for the same diastolic volume means a higher pressure This higher pressure can only be built up by an increased wall tension This indicates that diastolic relaxation is not complete and that the myofibrils are contracted to a certain degree during diastole This is also shown histologically Our electron microscopic observations showed contracture bands in myofibrils meaning that relaxation is not complete During contraction the myofibrils on the average seem to build up the same tension since the systolic stiffness is not altered by the shock meaning that for a given volume the same pressure is built up That this increase in diastolic pressure means a change in mechanical functioning was further shown by a decrease in the time derivative of left ventricular pressure Since preload was controlled and the hearts were beating isovolumically the contractility seems to be decreased by the shock [23] This may be explained by the fact that the myofibrils in the contracture band only take part in contraction for a small portion or not at all Thus fewer myofibrils can be fully activated

A critical remark should be made about our control values for the systolic and diastolic stiffness Our values are approximately a factor 10 higher than those reported for dog hearts [4]

This may be explained by the Laplace law whi describes the relationship between wall ten and pressure in a hollow organ as a function geometry and size From this law there follows inversely proportional relationship between st ness and volume Since the rabbit hearts we u are considerably smaller than dog hearts t may lead to higher stiffnesses in our case Also did not find an exponential relationship betw volume and pressure as did Glantz and Kernof We used only moderate volumes for which th curve is also linear Another factor may be th they used non perfused isolated hearts instead beating hearts as in this study

Our results indicate a change in mechani functioning if the energy exceeds 45 joules o density of 1 5 J /cm and a current density of amp /cm However this result was obtained i series of shocks and the 45 joules was preceded a 15 joule and by a 30 joule shock The study the influence of consecutive shocks showed i series of only 45 J shocks a progressing increase diastolic stiffness with shock number affirm the known correlation between necrosis and repetition of shocks The preceding shocks pro bly make the heart more susceptible to da age [7]

Besides electrical and mechanical functioni we also measured some biochemical paramete The coronary flow rate was temporarily increa after 15 and 30 joule shocks Since the coron flow rate is known as a determinant of oxidat metabolism in isolated perfused hearts this s gests a temporarily increased oxygen demand the heart Tentatively the vasodilation probal mediated by adenosine from ATP degradati can be explained by a response of the heart shocks by ATP consuming processes to resto the normal situation comparable to norm physiological response to enhanced exerci Shocks also caused an increased effluent to creatine kinase (CK) activity Enzyme depleti appears to be a biochemical indicator of t extent of myocardial damage The enzyme lease increased in value with increasing sho energy indicating a relationship between he intensity and damage The increased CK le after shocks with the same 15 J stored energy b applied through smaller electrodes shows that t densities of current and energy are more dam ing than total applied current and energy energy and current per gram heart weight

Since energy may damage the heart by heatir

Local temperature effects were less plausible because preliminary studies had shown that after 30 J shocks with saline soaked gauze covered electrodes improving the electrode heart contact CK activity was rather higher than lower in comparison with bare electrode shocks

Potassium Potassium depletion could be detected in the initial 40 seconds after both 15 and 30 J shocks by an increase from 4 7 to at most 5 1 mmol/L in 10 second samples ($n = 3$) Then the potassium surplus was washed out by increased flow making the differences with the initial concentration too small for measurement with the technique used

Coronary flow Simple pressing of the electrodes against the heart resulted in a small elevation of coronary flow rate After shocks flow decreased the first minute This decrease was larger for a shock induced temporary arrest than for a tachyarrhythmia The flow rate subsequently rose above the starting value between the second and fourth minute followed by a gradual return to the starting flow (Fig 7) This overshoot was higher for larger shocks

Discussion

Defibrillation pulses undoubtedly cause alterations in the electrophysiology and mechanical function of the isolated perfused rabbit heart Since our first goal was to develop an experimental model to study cardiac damage and to assess related parameters we shall first discuss our data relative to that

Many causes may influence a heart in an experimental defibrillation study but by using an excised perfused heart we could control coronary perfusion pressure PO of the perfusate temperature afterload preload and we could avoid the influence of anesthetic agents and reduce neural influence By applying synchronized shocks the effects of fibrillation could be avoided Although this model gives more control it is even further away from the normal physiological situation than an anesthetized animal is But it is useful to determine damage levels or compare damage caused by different shocks

The changes in parameters we used to assess damage caused by the shock require the following discussion

The duration of disturbance of the rhythm increased with shock energy but also the character of the disturbance changed since for moderate

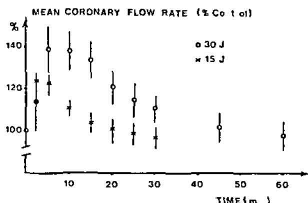


Fig 7 Mean coronary flow rate as a percentage of the control value prior to the shock after 15 ($n = 8$) and 30 ($n = 11$) joule shocks presented as a function of the time elapsed after shocks Mean values and standard error of the mean are indicated

shocks only some premature beats and short runs of tachycardia were noticed and for heavy shocks mostly a long duration arrest was seen

Those arrhythmias may be caused by a direct depolarizing action of the shock [5, 21] or by activation of nerve endings which may lead to changes in resting potential

Temporary changes in resting potential alter the permeability of the membrane to ions or vice versa The observed increase in extracellular potassium concentration after shocks indicates that the membrane has become more permeable to K ions which supports the idea of a change in membrane potential towards depolarization A moderate change in resting membrane potential may result in one premature beat if it lasts briefly or a run of tachycardia if the duration of the partial depolarization is longer No conclusive evidence exists about the cause of this partial depolarization It may be caused by the shock directly since the current being an ionic current in the heart requires a large amount of moving ions These transported ions may give rise to imbalances in electrical cell equilibrium resulting in a changed excitability But stimulation of sympathetic nerve endings may also change the cell s electrical equilibrium by release of transmitters acting on the membrane

A strong shock gives a long lasting arrest its duration increasing with shock energy This arrest may be caused by a total and enhanced depolarization after the shock which renders a cell inexcitable for the duration of the depolarization The enhanced depolarization is partly

shock Effect of paddle electrode size and time interval between discharge Circulation **50** 956 1974

4 Koning G Strength duration curves for direct ventricular defibrillation with rectangular current pulses Proceedings Cardiac Defibrillation Conference West Lafayette Indiana 1975 pp 75-80

5 Geddes L A Tacker W A McFarlane J and Bourland J Strength duration curves for ventricular defibrillation in dogs Circulation **27** 551 1970

6 Schuder J C Stoeckle H West J A and Keskar P Y Transthoracic ventricular defibrillation in the dog with truncated and untruncated exponential stimuli IEEE Trans on BME **18** 410 1971

7 Tacker W A Geddes L A and Hoff H E Defibrillation without A V block using capacitor discharge with added inductance Circ Res **22** 633 1968

8 Stoeckle H Nellis S H, and Schuder J C Incidence of arrhythmias in the dog following transthoracic ventricular defibrillation with unidirectional rectangular stimuli Circ Res **33** 343 1968

9 Warner E D Dahl C and Ewy G A Myocardial injury from transthoracic defibrillation countershock Arch Pathol **99** 55 1975

10 Davis J S Lie J T Bentinck D C Titus J L Tacker W A and Geddes L A Cardiac damage due to electric current and energy Light microscopic and ultrastructural observations of acute and delayed myocardial cellular injuries Proceedings Cardiac Defibrillation Conference West Lafayette Indiana 1975 pp 27 32

11 Ehsani, A Ewy G A and Sobel B E Effects of electrical countershock on serum creatine phosphokinase (CPK) isoenzyme activity Am J Cardiol **27** 12 1976

12 Shell W E and Sobel B E Biochemical markers of ischemic injury Circulation **53**(Suppl I) I 98 1976

13 Martino A Kissack A S Stuckey J H Kavaler F and Fischer V J Myocardial function after electrically induced ventricular fibrillation Am J Cardiol **24** 537 1969

14 Buckberg G D and Hottenrott Ventricular fibrillation Ann Thorac Surg **20** 76 1975

15 Antoni H Wirkungen des elektrischen Stroms auf die Grundprozesse der Erregung im Herzen Bull Schweiz Akad Med Wiss **31** 17 1975

16 Pansegrau D G and Abbout F M Hemodynamic effect of ventricular defibrillation J Clin Invest **49** 282 1970

17 Ross B D Perfusion Techniques in Biochemis[...] Oxford 1972 Clarenden Press pp 288 289

18 Meyler F L Over de mechanische activiteit van [...] geisoleerde volgens Langendorff doorstroomde zoogd[...] hart Ph D Thesis Amsterdam p 15 1960

19 Rosalki S B An improved procedure for serum creat[...] phosphokinase determination J Lab Clin Med 69 [...] 1967

20 Szasz G Gruber W and Bernt E Creatine kinase [...] serum I Determination of optimum reaction conditio[...] Clin Chem **22** 650 1976

21 Jones J L Lepeschin E Rush, S and Jones, [...] Depolarization induced arrhythmias following h[...] intensity electric field stimulation of cultured myo[...]dial cells (Abstract) Med Instr **12** 54 19 8

22 Van den Bos G C Elzinga G Westerhof N [...] Noble M I M Problems in the use of indices [...] myocardial contractility Cardiovasc Res 7 834 19[...]

23 Noble M I M Editorial Problems concerning [...] application of concepts of muscle mechanics to [...] determination of the contractile state of the hea[...] Circulation **45** 252 1972

24 Suga H and Sagawa K Instantaneous press[...] volume relationships and their ratio in the exci[...] supported left ventricle Circ Res **35** 117 1974

25 Templeton G H Ecker R R and Mitchel, J H [...] ventricular stiffness during diastole and systole [...] influence of changes in volume and inotropic st[...] Cardiovasc Res *6* 95 1972

26 Glantz S A and Kernoff R S Muscle stiff[...] determined from canine left ventricular pressure-volu[...] curves Circ Res **37** 787 1975

27 Stern S Sonnenblick M Keren A and Gottlieb [...] Positive technetium 99m stannous pyrophosphate [...] diac scan following elective cardioversion for atrial fib[...]lation (Abstract) Circulation **56** III 63 1977

28 Jennings R B and Ganote C E Mitochondrial str[...] ture and function in acute myocardial ischemic injur[...] Suppl I to Circ Res **38** 1 80 1976

29 Geddes L A Tacker W A Rosborough J Calder [...] Chapman R and Rivera R The increased efficacy [...] high energy defibrillation Med Biol Engineer[...] **14** 330 1976

30 Gutgesell H P Pediatric Defibrillation Proceedings [...] a Cardiac Defibrillation Conference West Lafaye[...] Indiana 1976 pp 65 66

IMPORTANT
INFORMATION FOR AUTHORS

All manuscripts for the AMERICAN HEART JOURNAL should be sent to

Dean T Mason M D
Section of Cardiovascular Medicine
University of California
School of Medicine
Davis California 95616

the effect of increased heart temperature on CK activity was also studied An increase of the perfusate temperature to 42° C caused significant CK activity To induce this temperature rise by shock energy it would require 158 J (6° C × 6 3 g heart) which is a factor 7 higher than the energy caused by the shock Thus it is not probable that the damage is caused by heating

The biochemical parameters indicate the first signs of detrimental influence of the shock intensity is a 2 1 J /cm density or a current density of 1 8 amp /cm²

Although we could demonstrate a change in parameters describing electrical or mechanical functioning of the heart and some biochemical parameters the difficulty remains to define damage because there are reversible irreversible and intermediate phases [6] and because reduction of tissue function may be caused by total failure and/or partial failure of cells In addition as a consequence of heterogeneity of the heart muscle destroying of cells of one type can be functionally more effective than death of the same amount of cells from other cardiac types Nevertheless without being able to describe a sharp borderline between damaged reversibly damaged and undamaged areas for the total heart we can conclude from this study that defibrillatory shocks may at least temporarily change cardiac function The first signs are seen at an energy density level of 0 8 J /cm² and accompanying current density of 0 5 amp /cm At levels of 2 1 J /cm and a current density of 1 8 amp /cm cellular damage could be proven as indicated by enzyme release

Extrapolating experimental results to the clinical environment has to be done very carefully From this study it would have been omitted if there was not the tendency to raise the defibrillator output for heavy subjects [2] whereas in pediatric cardiology no uniformity in dose concept has been attained [30]

On the basis of the above mentioned damaging doses no cardiac damage may be expected for normal internal defibrillation with energy up to 50 J and electrodes of 60 cm size

For external defibrillation the applied energy density is unknown Assuming the current density at the apex electrode (60 cm²) equals that in the part of the heart just below it normal external adult defibrillation using 400 J as the maximum energy seems to be safe using for instance 1 000 J may result in 1 5 amp /cm which in this study induced bradyarrhythmias In pediatric cardiology even the normal range up to 400 J may result in excessive energy density to the smaller electrodes (e g 15 cm) Estimation in advance of the tolerable energy for each electrode before its application seems to be recommended

Summary

The purpose of this study was to establish the damaging dose of defibrillator pulses The damage caused to isolated perfused rabbit hearts by synchronized defibrillator shocks with a stored energy from 15 up to 70 joules is reported The damage was characterized by the duration and severity of post shock arrhythmias changes in the elastic properties of the left ventricle the first derivative of left ventricular pressure morphological changes of the heart muscle elevation of creatine kinase potassium washout and a change in mean coronary flow rate Varying the electrode area showed that densities of applied current and energy are major factors in damaging the heart

At current and energy densities of 0 5 amp / cm² and 0 6 J /cm respectively potassium washout and mild arrhythmias are seen as is complete arrest of the ventricles at 1 2 amp /cm² and 1 5 J /cm² pulses After 1 8 amp /cm² irreversible cell damage occurs as demonstrated by CK release and also cardiac function is reduced measured by increased diastolic stiffness and decreased contractility Current and energy densities exceeding 2 5 amp /cm and 4 2 J /cm² respectively cause changes in cardiac function incompatible with life Accumulation of damage was observed with a series of 1 2 amp /cm² shocks

We are indebted to G P Tromp M D for carrying out preliminary experiments to F A Bekius for technical assistance and to Mrs A E Schwartz for preparing the manuscript The morphological examinations were done at the Department of Electron Microscopy of the Free University Amsterdam directed by Mrs E C M Hoefsmit Ph D who also interpreted the microscopic findings We gratefully thank G J Anderson M D Philadelphia for his valuable discussions

REFERENCES

1 Tacker W A Galioto F M Giuliani E Geddes L. A., and McNamara D Energy dosage for human trans chest electrical ventricular defibrillation N Engl J Med 290 214 1974
2 Resnekov L and McDonald L Complications in 220 patients with cardiac dysrhythmias treated by phased direct current shock and indications for electroversion Br Heart J 29 916 1967
3 Dahl C F, Ewy G A Warner E D and Thomas E D Myocardial necrosis from direct current counter

Table I Patient values for baseline VPB frequency and complexity and study VPB frequency complexity, and serum quinidine levels

	Baseline				Study					
Patient	*Age (yrs)*	*Q dose*	*VPB frequency (bts/hr)*	*VPB complexity*	*Response to Q*	*VPB complexity*	*Lowest VPB frequency (bts/hr)*	*Serum Q range during response (μg/ml)*	*Peak serum Q (μg/ml)*	*Trough serum Q (μg/ml)*
A	62	200 mg q6h	480 1800	M/P	N	None	16 94	–	1.96	1.56
B	58	200 mg q6h	720	P/VT	Y	4M/1P	14 8	0 88-1 44	1 44	0.56
C	67	200 mg q6h	600 2400	M/P	Y	2M/1/2P	52 40	0 72 1.28	1 65	0 65
D	60	200 mg q6h	45 205	M/P	Y	1/2P	0	2 90-4 50	4 50	2.50
E	66	200 mg q6h	30 120	M/VT	Y	None	0	1.50-2.10	2 10	1.50
F	65	200 mg q6h	480-600	None	Y	None	0	3 17 5 07	5 07	3 17
G	55	200 mg q6h	180-300	P	Y	None	0	2.20-3 40	3 40	2.20
H	61	200 mg q6h	900	M/P	N	5-1/2M/ 1 1/2VT 6P	184 146	–	2 50	1.89
		300 mg q6h	900	M/P	Y	2 1/2M/ 1 1/2P	0	2 80-4 25	4 25	2.80
I	45	300 mg q6h	300-720	M/P	N	4M/2 1/2P	124 58	–	2.15	1 38
J	81	300 mg q6h	900†	None†	Y	None	0	3 60-5 45	5 45	3 60
K	60	300 mg q6h	720-900	None	Y	None	0	2 14-4 17	4 17	2 14
L	81	300 mg q4h	120-500	P/VT	Y	1M/2P	8 8	5.27 5 92	6 17	5.27
M	62	400 mg q6h	600‡	M/P‡	Y	5 1/2M/3P 2 1/2VT	14 14	4 15-4 75	5 10	3 ,0
N	46	400 mg q6h	300-600	None	Y	None	0	2 46-2.82	2 8?	1 60

Abbreviations M = multiform N = no P = pairs (two VPBs in succession) Q = quinidine VPB = ventricular premature beat VT = three or more VPBs Y = yes.
= VPBs absent throughout study
† = Baseline observations obtained after discontinuation of quinidine
‡ = Baseline observations obtained whil patient was receiving quinidine 300 mg every 6 hours
= Occurrence of complex form of VPB at any time during baseline observations
= Number of hours during dosin interval in which a particular complex form of VPB was noted
= In patients without complete VPB suppression for at least one half hour interval, the values given are for the two consecuti e half hours lowest VPB frequency

miscellaneous forms of heart disease Four patients were in New York Heart Association Functional Class 3 or 4 Ten patients were being treated with digoxin and one with propranolol

All patients studied were hospitalized in the Coronary Care Unit of the Baltimore Veterans Administration Medical Center In 12 of the 14 patients oral quinidine sulfate was being initiated for the treatment of sustained ventricular arrhythmias In one patient (Patient J) quinidine was being discontinued because of the apparent cessation of ventricular arrhythmias after a ventricular demand pacemaker had been inserted to treat episodes of marked sinus bradycardia (33/minute) secondary to 2 1 sinoatrial block In another patient (patient M) with persisting ventricular ectopy at a quinidine dose of 300 mg every 6 hours the dose had been increased to 400 mg every 6 hours In all cases the dose of quinidine was selected by the physicians res ble for the clinical care of the patient W informed consent was obtained before the p was entered into the study

Serum quinidine concentration was deter immediately before and at 1 2 3 4 5 a hours after the study dose of quinidine quinidine assay employed was a specific method recently developed by one (W G C)[8,9]

The dose of quinidine was 200 300 or 40 every six hours in 13 patients and 300 mg four hours in one patient One patient was st at both 200 mg and 300 mg every six hou insure that a steady state had been attaine patients received quinidine for at least five lives prior to the study The mean in between baseline observations and initiati quinidine therapy was 1 8 days (range 1

Relation of ventricular premature beat suppression to serum quinidine concentration determined by a new and specific assay

Nathan H. Carliner M D
Michael L Fisher M D
William G Crouthamel Ph D
Prem K Narang M S
Gary D Plotnick M D
Baltimore Md

Ventricular premature beats (VPB s) have been identified as a risk factor for sudden death Sudden death is most often the result of ventric ular fibrillation Although it has not been estab lished that long term antiarrhythmic therapy can prevent ventricular fibrillation clinicians fre quently employ antiarrhythmic drugs to suppress VPB s in the hope that the risk of sudden ventric ular fibrillation will be decreased Although there is little question that quinidine suppresses VPB s effectively in many patients [5 7] it is not clear to what extent determination of the serum quin idine concentration can assist the clinician in planning optimal quinidine therapy

The present study explores the relationship between serum quinidine concentration and VPB frequency The quinidine assay employed is a high performance liquid chromatography (HPLC) method recently developed in our labo ratory that is specific for quinidine [8 9] Earlier quinidine assays lacked specificity and measured in addition to quinidine dihydroquinidine and a multitude of metabolites of unknown activity For example the widely used assay of Brodie and Udenfriend [10] which measures total fluorescence after precipitation of plasma proteins yields quinidine concentrations approximately twice those of the more specific extraction assay meth ods [1 3] Thus it has recently been pointed out that the relationship between serum quinidine concentration and therapeutic effect should be reassessed using more specific quinidine assays [14]

In a prior study utilizing the new HPLC assay we assessed the pharmacokinetic properties of quinidine in a group of hospitalized patients who were receiving the drug for the suppression of ventricular arrhythmias [5] As a part of that study serum quinidine concentrations were determined hourly during a dosage interval at steady state while the cardiac rhythm was documented by continuous Holter monitor tape recording VPB frequency and complexity prior to the initiation of quinidine therapy had been established by Holter recording or computer assisted oscilloscop ic monitoring We applied the rigorous criteria recently proposed by Winkle[16] to distinguish a true drug response from spontaneous variation in ventricular ectopy and identified the range of serum quinidine concentrations that were asso ciated with a therapeutic response defined in this manner

Methods

Fourteen patients (all males) are the subject of the present report (Table I) Their ages ranged from 45 to 81 years with a mean age of 62 years Eight patients had chronic ischemic heart disease Two patients had cardiomyopathy and four had

From the V terans Administration Med cal Ce ter and Uni ersity of Maryland Schools of Med cine and Pharmacy B ltim re

Supported in part by th Med cal Research Service of the V terans Administrat o

Rece ed f publication Apr 10 1979

Accepted f publicat n Dec 3 19 9

Reprint requests Nathan H C liner M D VA Medical Cent (151) 3900 Loch Ra n Bl d Baltimore Md 21 18

Results (Table I)

There was a therapeutic response to quinidine in 12 of 14 patients. In four of these 12 patients there was total VPB suppression. The remaining eight responders demonstrated 90% VPB suppression that persisted for at least two consecutive half hour segments during the steady state dosing interval of 4 to 6 hours. Four of these eight patients had no VPBs during at least one half hour segment of the dosing interval.

In the ten patients who did not have total VPB suppression at steady state, we looked for a correlation between serum quinidine concentration and VPB frequency. (Since patient H was studied at two dosage levels, 11 dosing intervals were analyzed.) Considering the ten patients as a group, we could find no correlation between serum quinidine concentration and VPB frequency during the dosing intervals at steady state. The mean serum quinidine concentration at the time of the lowest VPB frequency during the dosing interval (2.93 ± 1.48 μg/ml) did not differ significantly from that at the time of highest VPB frequency (2.77 ± 1.56 μg/ml). However, in seven individual dosing intervals there was a tendency for VPB frequency to decrease as the serum quinidine concentration increased.

We compared the seven steady state dosing intervals in which at least one half hour segment was completely free of VPBs with the remaining eight dosing intervals in which there was no half hour that demonstrated complete suppression. Both the mean and peak serum quinidine levels tended to be higher for the dosing intervals with at least one half hour of complete VPB suppression (mean = 3.14 ± 0.87 μg/ml, peak = 3.97 ± 1.13 μg/ml) than for those without this finding (mean = 2.55 ± 1.78 μg/ml, peak = 3.00 ± 1.86 μg/ml). However, these differences were not statistically significant.

Multiform VPBs were present in eight responders at baseline but were absent in these patients in 47% of the half hour segments monitored during steady state therapy. Paired VPBs were present in nine responders at baseline but were absent in 68% of the half hour segments at steady state. Salvos of three or more VPBs were present in three responders prior to quinidine therapy but did not occur in any of the half hour segments monitored during therapy in these three patients.

Using the new HPLC quinidine assay, the range of serum quinidine concentrations asso[ciated] with a therapeutic response at steady stat[e] in our patients was 0.72 to 5.92 μg/ml. Three [of] the 12 responders demonstrated a response a[t] serum levels of less than 2.0 μg/ml and two of th[e] three responded at a level of less than 1.0 μg/m[l]. During the three dosing intervals in which [a] definite therapeutic response to quinidine cou[ld] not be identified, the serum quinidine concentra[tions] ranged from 1.38 to 2.50 μg/ml.

Patient H was studied after the initial 200 m[g] dose of quinidine and at steady state at doses [of] 200 and 300 mg every 6 hours. Fig. 1 demon[strates] the lack of a response after the initial 20[0] mg dose (mean serum Q = 0.64 μg/ml). On [a] regimen of 200 mg every 6 hours, a response coul[d] not be documented at steady state (mean seru[m] Q = 2.09 μg/ml); however, when the dose wa[s] increased to 300 mg every 6 hours, there wa[s] clearly a response at steady state (mean seru[m] Q = 3.50 μg/ml).

Discussion

In order to assess the usefulness of seru[m] quinidine concentrations in the management [of] patients with ventricular arrhythmias, the fo[l]lowing conditions should be met:

1. The quinidine assay employed should b[e] specific for quinidine and should not includ[e] contaminants and metabolites. Unfortunately, many earlier studies employed assays that we[re] not specific for quinidine.[5, 6, 11, 17, 18]

2. There should be a quantitative estimate o[f] the degree of VPB suppression. It is of interes[t] that some of the reported therapeutic ranges fo[r] quinidine concentration were determined solel[y] in patients with atrial fibrillation.[7] In tho[se] studies which deal with the response of ventricu[lar] arrhythmias to quinidine therapy, varyin[g] criteria have been used to determine efficacy. Fo[r] example, Kessler and associates[11] considered [a] decrease in premature contractions to be evi[dence] of clinical effectiveness, but no data ar[e] provided concerning VPB frequency either befor[e] or during quinidine therapy. Gaughan and col[leagues][6] studied the response to a single 0.6 g[m] dose of quinidine. They defined a positiv[e] response as a 50% or greater reduction in VPB[s] and abolition of repetitive beats. However, it ha[s] recently been pointed out that because of th[e] marked spontaneous variation in the degree o[f] ventricular ectopy,[1-4] a 90% reduction in VPB

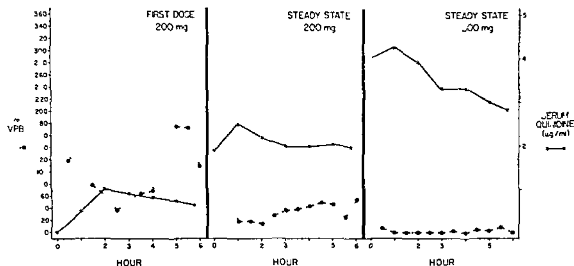


Fig 1 Serum quinidine concentration *(solid line)* and percent of baseline ventricular premature beat *(VPB)* frequency *(dotted line)* in Patient H during a 6-hour dosing interval after the initial 200 mg of quinidine at steady state on a regimen of quinidine 200 mg every 6 hours and at steady state on a regimen of quinidine 300 mg every 6 hours. A therapeutic response to quinidine as defined in this paper is present only at a dose of 300 mg every 6 hours.

days) The mean interval between baseline observations and observations at steady state was 5 8 days (range 2 to 14 days)

Winkle s criteria [6] were used to determine if a therapeutic response to quinidine was present During steady state quinidine therapy there had to be complete VPB suppression for a half hour or 90% suppression compared to the baseline frequency that was maintained for at least two consecutive half hour segments of the dosing interval When the recorded baseline VPB frequency varied the lowest frequency was used in the calculation of percent suppression at steady state The results were analyzed to determine the range of serum quinidine concentrations that was associated with a definite therapeutic response

Baseline VPB frequency and complexity were determined by Holter monitoring in three patients and by computer assisted CCU oscilloscopic monitoring in 11 patients In all 14 patients cardiac rhythm was recorded on a Holter monitor during the steady state dosing interval selected for study Sequential 30 minute segments of the recording were analyzed to determine the total number of VPB s in each segment Each half hour segment was also analyzed for the presence or absence of the following complex forms of VPB s multiform pairs and salvos of three or more

In the 12 patients being started on quinidine baseline observations of VPB frequency and complexity were made prior to the start of quinidine therapy In patient J the baseline was established after the discontinuation of quinidine In patient M the baseline was established at a dose of 300 mg every 6 hours and the study was carried out at a dose of 400 mg every 6 hours

In the 14 patients who are the subject of the present report the baseline VPB frequency ranged from 30 to 2 400 per hour In only two of the patients was the lowest recorded baseline VPB frequency less than 60 per hour In these two patients (Patients D and E) VPB frequency ranged from 45 to 205/per hour and from 30 to 120/per hour respectively Because the VPB frequency in these patients most often was greater than 60 per hour they are included along with the other 12 patients in the analysis of therapeutic response Thus an average baseline VPB frequency of at least one per minute was required for inclusion in the study

The effect of quinidine on complex forms of VPB s was assessed in the patients who were classified as responders according to Winkle s criteria For those responders with multiform VPB s, pairs or salvos of three or more VPB s at baseline we determined the percent of half hour segments during the steady state quinidine dosing interval in which each of these complex forms was absent

Data were analyzed using non paired t tests and linear regression analyses

be shown for an entire patient group there appears to be a tendency in individual patients for VPB frequency to be lower at higher serum quinidine levels Therefore if VPBs are not controlled at a serum quinidine level within the therapeutic range the dose may be increased unless there is evidence of quinidine toxicity

Summary

Fourteen patients who were receiving quinidine in doses of 800 to 1800 mg per day for ventricular arrhythmias underwent Holter monitoring during a steady state dosing interval at a mean of four days after the initiation of quinidine therapy Serum quinidine concentration determined by a specific high performance liquid chromatography method was measured hourly during the dosing interval Ventricular premature beat (VPB) frequency during quinidine therapy was compared to the baseline VPB frequency A reduction in VPB frequency of at least 90% was required to substantiate the presence of a therapeutic response to quinidine

In 12 of the 14 patients a therapeutic response to quinidine was present at serum levels ranging from 0 72 to 5 92 μg/ml There was no group correlation between serum quinidine concentration and VPB frequency but there was a tendency in individual patients for VPB frequency to decrease as serum quinidine level increased Quinidine toxicity was not observed in these 14 patients

Because of the wide variation in response to quinidine a serum quinidine concentration that is within the therapeutic range is not necessarily the optimal serum quinidine concentration for an individual patient The clinician may therefore consider increasing the dose if there is no evidence of quinidine toxicity and the ventricular rhythm disturbance is not adequately controlled

We wish to express our appreciation to Ms Georgette Frank and Mr Gary Shayne for their expert technical assistance and to Mrs Helen Spencer and Mrs Patricia Weinel for typing the manuscript

REFERENCES

1 Chiang B N Perlman L V Fulton M Ostrander L D and Epstein F H Predisposing factors in sudden cardiac death in Tecumseh Michigan Circulation 41 31 1970
2 Vismara L A Vera Z Foerster J M, Amsterdam E A and Mason D T Identification of sudden death risk factors in acute and chronic coronary artery disease Am J Cardiol 39 821 1977
3 Ruberman W Weinblatt E Goldberg J D Frank C W and Shapiro S Ventricular premature beats and mortality after myocardial infarction N Engl J Med 297 750 1977
4 Han J and Goel B G Electrophysiologic precursors of ventricular tachyarrhythmias Arch Intern Med 129 749 1972
5 Jelinek M V Lohrbauer L and Lown B Antiarrhythmic drug therapy for sporadic ventricular ectopic arrhythmias Circulation 49 659 1974
6 Gaughan C E Lown B Lanigan V Voukydis P and Blaser H W Acute oral testing for determining antiarrhythmic drug efficacy Am J Cardiol 38 677 1976
7 Winkle R A Gradman A H and Fitzgerald J W Antiarrhythmic drug effect assessed from ventricular arrhythmia reduction in the ambulatory electrocardiogram and treadmill test Comparison of propranolol, procainamide and quinidine Am J Cardiol 42 473 1978
8 Crouthamel, W G, Kowarski B Narang P K Specific serum quinidine assay by high performance liquid chromatography Clin Chem 23 2030 1977
9 Crouthamel W G Kowarski B and Narang P K Chromatographic behavior of 3 hydroxyquinidine (Letter) Clin Chem 24 1853 1978
10 Brodie B B and Udenfriend S The estimation of quinine in human plasma with a note on the estimation of quinidine J Pharmacol Exp Therap 78 154 1943
11 Kessler K M, Lowenthal D T, Warner H Gibson T Briggs W and Reidenberg M M Quinidine elimination in patients with congestive heart failure or poor renal function N Engl J Med 290 706 1974
12 Hartel G and Harjanne A Comparison of two methods for quinidine determination and chromatographic analysis of the difference Clin Chim Acta 23 289 1969
13 Hartel, G and Korhonen A Thin layer chromatography for the quantitative separation of quinidine and quinidine metabolites from biological fluids and tissues J Chromatogr 37 70 1968
14 Woosley R L and Shand D G Pharmacokinetics of antiarrhythmic drugs Am J Cardiol 41 986, 1978
15 Carliner N H Crouthamel W G Fisher M L Mugmon M A Vassar D I Narang P K and Plotnick G D Quinidine therapy in hospitalized patients with ventricular arrhythmias, Am Heart J 98 708 1979
16 Winkle R A Antiarrhythmic drug effect mimicked by spontaneous variability of ventricular ectopy Circulation 57 1116 1978
17 Bloomfield S S Romhilt D W Chou T C and Fowler N O Quinidine for prophylaxis of arrhythmias in acute myocardial infarction N Engl J Med 285 979 1971
18 Gey G O Levy R H Pettet, G and Fisher L Quinidine plasma concentration and exertional arrhythmia Am Heart J 90 19 1975
19 Sokolow M and Ball R E Factors influencing conversion of chronic atrial fibrillation with special reference to serum quinidine concentration Circulation 14 568 1956
20 Morganroth, J Michelson E L, Horowitz, L N Josephson M E, Pearlman A S and Dunkman, W B Limitations of routine long term electrocardiographic monitoring to assess ventricular ectopic frequency Circulation 58 408 1978

frequency should be required to substantiate the presence of a true drug effect[7, 16]

Quinidine assay The quinidine assay used in this study is a new and specific HPLC method[8] which excludes the known metabolites of quinidine Although there is evidence that these metabolites may have antiarrhythmic activity in mice and rabbits activity has not yet been demonstrated in man and in man the serum concentration of these metabolites is generally below that of quinidine[21]

Analysis of therapeutic response The marked spontaneous variability of ventricular arrhythmias has been emphasized recently by a number of investigators[7, 16, 20] This factor must be taken into account before an observed decrease in ventricular ectopic activity can be accepted as evidence of a drug effect Winkle[1] has recently proposed rigorous criteria which are applicable in the clinical setting to differentiate a true drug response from spontaneous variation in VPB frequency These criteria were met in 12 of the 14 patients in the present study For the patients classified as responders according to Winkle s criteria complex forms of VPB s (multiform pairs or salvos of three or more) present during baseline observations were absent in from 47% to 100% of the half hour intervals monitored during steady state therapy As there appears to be even greater spontaneous variability in VPB complexity than in frequency[6] a decrease in complex forms during quinidine therapy was not considered sufficient in itself to establish the presence of a therapeutic response

Relationship between serum quinidine level and VPB suppression Because of the marked differences that exist among patients with arrhythmias our failure to demonstrate a correlation between serum quinidine level and VPB frequency in the entire group of patients is not surprising and is consistent with the experience of other investigators[5, 6] As each patient was not studied at multiple dosage levels we cannot comment on whether a dose response relationship would pertain in individual patients In patient H (Fig 1) such a response was demonstrable It is of interest that both mean and peak serum quinidine levels tended to be higher during dosing intervals with at least one half hour of complete VPB suppression than in dosing intervals without this finding and in seven of 11 steady state dosing intervals there was a tendency for VPB frequency to decrease as serum quinidine level increased

The range of therapeutic serum quinidine concentrations extended from 0 72 to 5 92 μg/ml No patient in the present study manifested quinidine toxicity but one patient seen in consultation demonstrated new intraventricular conduction defects at an estimated peak serum quinidine concentration of 6 3 μg/ml Three patients responded at levels of less than 2 0 μg/ml and two of the three responded at a level of less than 1 0 μg/ml Lown s group has also described patients who show a therapeutic response to quinidine at serum levels of less than 2 0 μg/ml

It should be emphasized that the therapeutic range in the present study applies only to VPB suppression as there were no patients with atrial arrhythmias in the study group In addition the serum quinidine concentrations that were used to establish the therapeutic range were those associated with a definite drug response even if the response was not considered optimal by the clinician treating the patient. Some patients with symptomatic ventricular tachycardia may require maximal tolerated doses of antiarrhythmic drugs with resultant high serum levels to prevent recurrences[22] Thus we agree with Lown s group that the presence of a serum quinidine concentration that is within the therapeutic range should not deter the clinician from increasing the dose if necessary to gain better control of the arrhythmia[23] This is illustrated by our patient H (Fig 1) in whom a drug response was not present at mean serum quinidine concentrations of 0 64 and 2 09 μg/ml but was clearly evident when the dose was increased resulting in a higher mean serum quinidine concentration of 3 50 μg/ml A similar phenomenon has been reported by other investigators[6, 18]

Conclusions

1 The range of serum quinidine levels at which a decrease in VPB frequency could be demonstrated in our patients was 0 72 to 5 92 μg/ml using a specific HPLC quinidine assay

2 Because of the variations that exist among individuals with arrhythmias there is no optimal serum quinidine level at which maximal control of ventricular rhythm disturbances can be expected in all patients

3 Although a significant correlation between serum quinidine level and VPB frequency cannot

Isovolumic relaxation period in man

Basil S Lewis M D M R C P F C P (S A)*
Noga Lewis B Sc
Dan Sapoznikov M Sc Ph D
Mervyn S Gotsman M D F R C P F A C C
Jerusalem Israel

Early diastolic relaxation and compliance of the left ventricle the abnormal in many cardiac diseases The rate of fall of left ventricular pressure the rate of ventricular filling and the geometrical changes which occur in the left ventricle and its wall during early diastole have been studied in patients with coronary artery and other cardiac diseases[1-5] these measurements are useful but require invasive cardiac catheterization or computer processing of echocardiographic data

The duration of the isovolumic relaxation period (IRP) is a simple parameter, but true IRP has been difficult to measure accurately[6-9] We have used echocardiography and phonocardiography to measure true IRP in normal subjects and in a large group of patients with different cardiac diseases to study its determinants and to evaluate its use as a simple noninvasive measarement of cardiac dynamics in terms of the present approach to ventricular relaxation and compliance

Patients

Eighty three patients with different cardiac diseases were studied They were divided into eight groups

1 **Normal subjects** Ten patients were referred for echocardiography because of the presence of a soft systolic murmur Their history physical examination electrocardiogram chest x ray and echocardiogram were normal and the diagnosis was that of an innocent systolic murmur

2 **Hypertension** Fifteen patients had sys- temic arterial hypertension with a diastolic blood pressure consistently above 90 mm Hg Patients with known coronary artery disease (previous infarction angina pectoris or diagnostic ischemic ECG changes) were not included in the group

3 **Coronary artery disease (CAD)** Fifteen patients with coronary artery disease were studied One patient had minor symptoms after an episode of myocardial infarction (NYHA Class 1) six were in Functional Class 2 five in Class 3, and three in Class 4 due to severe shortness of breath and left heart failure The diagnosis of CAD was confirmed in all patients by cardiac catheterization and coronary angiography In seven patients additional functional mitral incompetence was present and was confirmed by left ventriculography moderate or severe func tional mitral incompetence was found in fo r and mild or trivial incompetence was seen in three

4 **Hypertrophic cardiomyopathy** Nine pa tients had hypertrophic cardiomyopathy (HOCM) The diagnosis was made on the history physical examination and electrocardiogram and was confirmed by echocardiography

5 **Congestive cardiomyopathy (CMO)** Seven patients presented with a large heart and severe cardiac failure The etiology was viral myocardi tis in three patients and daunorubicin toxicity in two in the other two patients the etiology was uncertain but the disease probably followed a previous viral infection

6 **Aortic stenosis (AS)** Four patients had severe aortic stenosis confirmed by cardiac cathe terization The peak systolic gradient across the aortic valve ranged from 70 to 110 mm Hg

From the Cardiology Department H dassah Hosp tal, and the Hebrew University Jerusalem Isra l

Received for publication Ma 3 19 9
Accepted for publicat on July 20 1979

Reprint requests Dr B S Lewis Cardiology Dept H dassah Hospi tal, Jerusalem Isr el

Dr Lewis is the recipient of a Nathan Sa hs Award

0002-8703/80/100490 + 10$01 00/0 © 1980 The C V Mosby Co

21 Drayer D E Lowenthal D T Restivo K M Schwartz, A Cook C E and Reidenberg M M Steady state serum levels of quinidine and active metabolites in cardiac patients with varying degree of renal function Clin Pharmacol Ther 24 31 1978
22 Winkle R A Alderman E L Fitzgerald J W and Harrison D C Treatment of recurrent symptomatic ventricular tachycardia Ann Intern Med. 85 1 1976
23 Lown B and Graboys T B Management of patients with malignant ventricular arrhythmias, Am J Cardiol. 39 910 1977

Copyright information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner s consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients This consent is given on the condition however that the copier pay the stated per copy fee through the Copyright Clearance Center Inc 21 Congress Street Salem Mass 01970 617 744 3350 for copying beyond that permitted by Sections 107 or 108 of the U S Copyright Law This consent does not extend to other kinds of copying such as copying for general distribution for advertising or promotional purposes for creating new collective works or for resale For reprint quantities of 50 or more, contact Publisher

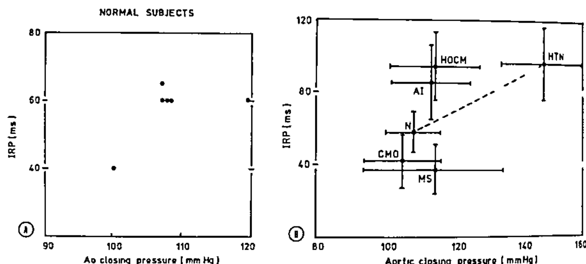


Fig 2 Relation between aortic closing pressure and isovolumic relaxation period (IRP) in normal subjects *(A)* (r = 0 65 p < 0 05) and in different cardiac diseases *(B)* IRP is prolonged in hypertrophic cardiomyopathy *(HOCM)* and in aortic incompetence *(AI)* and shortened in congestive cardiomyopathy *(CMO)* and mitral stenosis *(MS)*

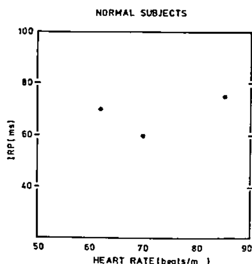


Fig 3 Relation between heart rate and isovolumic relaxation period *(IRP)* in normal subjects (r = 0 50 ns) IRP tended to increase with increasing heart rate

$$\text{ICT (msec)} = \text{PEP} - (\text{Q}_{\text{ECG}} - \text{C point}_{\text{ECHO}})$$

The point of mitral leaflet coaption was not defined clearly in all patients ICT was not measured in patients in whom the quality of the recording was inadequate

8 Blood pressure The blood pressure (BP) was recorded with a baumanometer at the time the study was performed Aortic closing pressure (AoCP) was the systolic pressure minus one third the pulse pressure

Statistical analysis Comparison of the data between groups of patients was made using Student s t test for unpaired data Correlation of data sets was sought using a least squares fit linear regression analysis Multiple regression analysis was used to derive an equation for predicted IRP in normal subjects

Results

The results are summarized in Tables I and II

IRP True IRP was 58 ± 11 msec in normal subjects It was prolonged in hypertension (p < 0 001), HOCM (p < 0 001) aortic stenosis (p < 0 05) and aortic incompetence (p < 0 01) and was shortened in congestive cardiomyopathy (p < 0 05) and in mitral stenosis (p < 0 01) In coronary artery disease IRP was normal or slightly increased (ns) The patients could be divided into two groups (Table III) six patients with CAD who had normal over all LV function (% ΔS > 25%) had a prolonged IRP (85 ± 10 msec) (p < 0 001) while nine patients with decreased over all systolic function (% ΔS ≤ 25%) had a normal IRP (59 ± 30 msec)

Patients with CAD were also divided into three groups according to the duration of the IRP four patients had a shortened IRP (< 50 msec) (group 1) one patient had a normal IRP (50 to 69 msec) (group 2) and 10 had a prolonged IRP (70 msec or more) (group 3 Table III) All four patients in group 1 had extensive LV damage (global LV dysfunction on LV angiography) and all had moderate to severe additional functional

7 Aortic incompetence (AI) In 11 patients the diagnosis was aortic incompetence Patients with additional mitral or other valve disease were not included in this group

8 Mitral stenosis (MS) Twelve patients with pure mitral stenosis were studied The diagnosis was made in nine patients by careful clinical examination ECG chest x ray and echocardiography In three patients cardiac catheterization was performed to exclude suspected disease of another valve in the other patients the diagnosis was clear and we felt that it was not ethically justified to catheterize the patient

Methods

Echocardiograms were recorded with an Ekoline 20A echocardiograph coupled to an Electronics for Medicine VR 6 or VR 12 photographic recorder A 2 25 MHz focused transducer was used and recordings were made from the standard interspace along the left sternal border M mode sweeps were made in the long axis of the left ventricle and the remainder of the echocardiogram was recorded in standard fashion A simultaneous phonocardiogram was recorded from the second and third left interspace or near the cardiac apex using an Electronics for Medicine piezoelectric crystal transducer The aortic component of the second heart sound was clearly shown in all the tracings A paper speed of 100 mm /sec was used to record time interval measurements

The following measurements were made

1 True isovolumic relaxation period (IRP) IRP was measured from the onset of the first high frequency deflection of the aortic component of the second heart sound on the phonocardiogram to the point of opening of the mitral leaflets on the echocardiogram Only tracings in which the point of separation of the leaflets of the mitral valve was clearly visible were used in the study (Fig 1)

2 Anterior mitral leaflet (AML) opening time (DE time) The DE time was measured from the onset of mitral leaflet opening (point D) to the peak anterior open position (E point) of the anterior mitral leaflet

3 Total time A –E point This was the sum of true IRP and the DE time In patients with mitral stenosis the measurement corresponds to the A_2–opening snap time

4 Mitral EF slope The steepest recorded

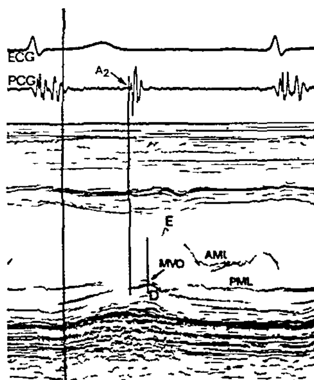


Fig 1 Electrocardiogram *(ECG)* phoncardiogram *(PCG)* and echocardiogram in a normal subject Isovolumic relaxation period is the time interval between the onset of the high frequency component of the aortic component of the second heart sound (A) to the point of separation of the mitral leaflets (*MVO D* point)

mitral EF slope was measured where possible where the EF slope was monophasic to avoid ambiguity in measurement [11]

5 PR AC time The time of closure of the AML (AC) was measured and subtracted from the PR interval of the electrocardiogram this corrects for changes in the PR interval of the electrocardiogram

6 LV dimensions and percentage shortening during systole Left ventricular diastolic diameter (Dd) systolic diameter (Ds) and the percentage shortening during systole (% ΔS) were measured in the standard plane of the M mode echocardiographic sweep at the level of the edge of the mitral leaflets or their chordae tendineae

7 Isovolumic contraction time (ICT) was measured by subtracting the time interval from the onset of the QRS complex of the electrocardiogram to the point of mitral coaption on the echocardiogram (C point) from the pre-ejection period (PEP) (measured in standard fashion from a carotid pulse tracing)

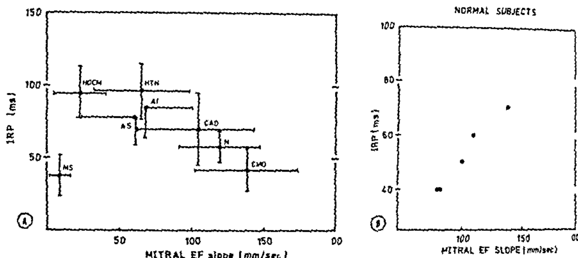


Fig 4 A Mitral EF slope and isovolumic relaxation period (IRP) in different cardiac diseases IRP is prolonged in diseases associated with a reduced EF slope and short in congestive cardiomyopathy (CMO) where the EF slope is increased In mitral stenosis (MS) both the EF slope and IRP are decreased B IRP tends to increase with increasing EF slope in normal subjects (r = 0 54 ns)

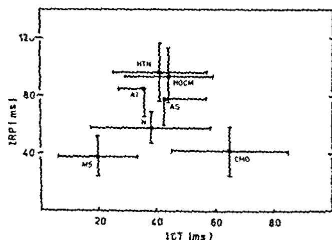


Fig 5 Isovolumic contraction time (ICT) and isovolumic relaxation time (IRP) in different cardiac diseases In mitral stenosis (MS) both ICT and IRP are reduced while in congestive cardiomyopathy (CMO) ICT is prolonged and IRP is shortened In aortic incompetence (AI) aortic stenosis (AS) hypertrophic cardiomyopathy (HOCM) and hypertension (HTN) IRP is prolonged with no change or with a small increase in ICT

heart rate IRP was related to aortic closing pressure in normal subjects ($r = 0\ 65$ $p < 0\ 05$) (Fig 2) and increased in patients with systemic hypertension Patients with HOCM and aortic incompetence fell upwards and to the left on the graph (Fig 2) indicating prolongation of the IRP for any given BP Patients with MS and CMO had a short IRP for their blood pressure

IRP increased slightly with increasing heart rate in normal subjects ($r = 0\ 50$ ns) (Fig 3) one patient disturbed the statistical relationship

Multiple regression analysis correlating IRP with aortic closing pressure (AoCP) and heart rate (HR) in normal subjects greatly improved the correlation coefficient ($R = 0\ 85$ $p < 0\ 001$) compared with the correlation coefficients for each of these variables taken independently and provided the following equation for predicted IRP

$$IRP = 0.97\ AoCP + 0\ 62\ HR - 86\ 6$$

Using this equation the deviation of the measured IRP from predicted normal (ΔIRP) was calculated in each patient The mean ΔIRP for each patient group is given in Table IV Measured IRP was prolonged in HOCM and AI ($+\Delta IRP$) was short in CMO and MS ($-\Delta IRP$) and normal in hypertension and CAD although there was considerable individual variation in each group so that the standard deviations were high

DE time The DE time measured 58 ± 17 msec in normal subjects It was normal in hypertension in CAD (all groups) in CMO AS and AI and was prolonged in HOCM ($p < 0\ 05$) and was shortened in MS ($p < 0\ 01$)

A_2 E point The duration A_2–E point was 116 ± 13 msec in normal subjects (Table II) It was prolonged in hypertension ($p < 0\ 01$) aortic stenosis (ns) and aortic incompetence ($p < 0\ 01$) and was greatly increased in HOCM ($p < 0\ 001$) In CAD the A_2–E point time was increased especially in patients with normal systolic function (% $\Delta S > 25\%$) ($p < 0\ 001$) The A_2–E point time was slightly shortened in CMO (ns) and was greatly shortened in MS ($p < 0\ 001$) There was

Table I Echocardiographic measurements in diastole

	No	True IRP msec	DE time msec	A E point msec	Mitral EF slope mm/sec	PR–AC msec
Normal subjects	10	58 ± 11	58 ± 12	116 ± 13	119 ± 29	70 ± 7
Hypertension	15	96 ± 20	55 ± 18	151 ± 32	65 ± 34	58 ± 18
Coronary artery disease	15	69 ± 17	59 ± 20	128 ± 36	104 ± 40	41 ± 24
Hypertrophic cardiomyopathy	9	94 ± 19	72 ± 14	167 ± 25	23 ± 19	69 ± 14
Congestive cardiomyopathy	7	42 ± 17	59 ± 21	101 ± 30	138 ± 36	54 ± 32
Aortic stenosis	4	78 ± 21	64 ± 41	141 ± 52	61 ± 45	70 ± 27
Aortic incompetence	11	85 ± 22	54 ± 12	139 ± 20	68 ± 32	73 ± 35
Mitral stenosis	12	38 ± 14	40 ± 15	77 ± 20	9 ± 7	–

See text for details of indices and abbreviations
$p < 0.05$
$p < 0.01$
$p < 0.001$

Table II Measurements of systolic LV function

	LVDd cm.	LVDs cm	% ΔS	ICT msec	Ao closing pressure mm Hg	Heart rate beats/min
Normal subjects	5.0 ± 0.3	3.2 ± 0.2	37 ± 4	38 ± 22	107 ± 8	67 ± 10
Hypertension	4.5 ± 0.7	2.8 ± 0.7	38 ± 11	41 ± 16	146 ± 18	74 ± 10
Coronary artery disease	5.9 ± 0.9	4.5 ± 1.2	24 ± 11	36 ± 19	116 ± 13	87 ± 14
Hypertrophic cardiomyopathy	4.4 ± 0.6	2.2 ± 0.4	49 ± 6	44 ± 15	113 ± 13	68 ± 14
Congestive cardiomyopathy	6.8 ± 1.2	5.8 ± 1.1	15 ± 7	65 ± 23	105 ± 11	92 ± 17
Aortic stenosis	4.6 ± 0.4	3.0 ± 1.0	34 ± 15	42 ± 15	–	65 ± 4
Aortic incompetence	6.3 ± 0.6	4.2 ± 0.7	33 ± 7	36 ± 9	112 ± 11	65 ± 16
Mitral stenosis	4.7 ± 0.8	3.1 ± 0.6	36 ± 3	20 ± 14	117 ± 21	76 ± 14

See text for details of indices and abbreviations
$p < 0.05$
$p < 0.01$
$p < 0.001$

mitral incompetence Group 1 echocardiograms showed great LV enlargement (Dd 6.3 ± 0.6 $p < 0.001$) and a low % ΔS ($p < 0.001$) Sinus tachycardia was present The single patient in group 2 (normal IRP) also had severe left ventricular enlargement and LV dysfunction but was hypertensive this may have increased his IRP so that it was not shortened as in the other patients with severe LV dilatation and LV dysfunction In contrast patients in group 3 (prolonged IRP) had mild LV enlargement (Dd 5.6 ± 0.4 $p > 0.05$) and a slightly decreased LV shortening fraction (mean % ΔS 27 ± 12 $p < 0.05$) although eight patients in group 3 had suffered previous infarction with regional ventricular asynergy and three had mild or trivial functional mitral incompetence LV end diastolic pressure (25 ± 10 mm Hg) was increased less than in group 1 (40 ± 6 mm Hg)

Relation of IRP to systemic blood pressure and

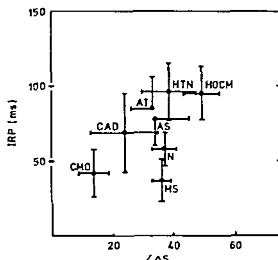


Fig 6 Systolic shortening fraction *(% ΔS)* and isovolumic relaxation period *(IRP)* in normal subjects *(N)* and in different cardiac diseases % ΔS and IRP increased or decreased in parallel, except in mitral stenosis *(MS)* where IRP was markedly shortened

different cardiac diseases are shown in Fig 5 In hypertension HOCM AI and AS IRP increased with no or little change in ICT in MS both IRP and ICT were short while in CMO IRP was short and ICT was prolonged

2 LV shortening fraction (% ΔS) IRP was related to percentage shortening of the LV in systole (Fig 6) In general in diseases where % ΔS was high IRP was prolonged patients who had a lower % ΔS had a shorter IRP In MS IRP was short for the % ΔS

Discussion

Echocardiography permits accurate measurement of the true isovolumic relaxation period of the left ventricle Our values for IRP (58 ± 11 msec) are shorter than those of most previous studies which used older methods to mark the end of the IRP invasive cardiac catheterization[6] angiographic studies the O point of the apexcardiogram and phono Doppler measurements[16] A previous echocardiographic study used the onset of rapid opening of the anterior mitral leaflet to mark the end of the IRP[17 18] We measured IRP from aortic closure to the point of separation of the mitral leaflets on the echocardiogram we believe that the point of separation of the leaflets is less ambiguous and conceptually more correct as a marker of the end of the true IRP Echocardiography also permits measurement of the mitral valve opening time DE and the time A_2—maximum mitral opening (E point)[1] a

Table IV Deviation of IRP from predicted normal values in cardiac disease (msec)

Normal subjects	0 6
Hypertension	–9 [illegible]
Hypertrophic cardiomyopathy	+ 1 ± 29
Congestive cardiomyopathy	–30 [illegible]
Aortic incompetence	+21 ± [illegible]
Mitral stenosis	–31 ± 21
Coronary artery disease	
– % ΔS > 25%	+3 [illegible]
– % ΔS ≤ 25%	–5 ± 29

Mean ± SD

measurement previously possible only in patien with mitral stenosis and an opening snap or with a prosthetic mitral valve producing an audible opening click

Isovolumic relaxation period is the time interval from aortic valve closure to mitral opening and depends on the aortic closing pressure the height of the v wave in the left atrium (mitral opening pressure) and the rate of pressure fall in the left ventricle (Fig 7) IRP may also be heart rate dependent and tends to increase in normal subjects with increasing heart rate In contrast to previous work using older methods for measuring IRP[14] our study shows an important relation to systemic blood pressure in normal subjects and use of the multiple regression analysis (correcting for heart rate and blood pressure) improved the relationship significantly Multiple regression analysis provided us with an equation for predicting IRP which may be useful in assessing isovolumic relaxation time in cardiac disease We did not measure left atrial pressure but IRP is very short in mitral stenosis and especially short in patients with CAD and important additional functional mitral incompetence The rate of LV pressure fall in early diastole (i e early diastolic relaxation of the LV) is also a determinant of IRP the greatly increased IRP and ΔIRP observed in patents with HOCM and the increase in IRP in patients with AS may be due to the mechanism, since both diseases are associated with high LV chamber stiffness as a consequence of severe LVH[5 2 2] In systemic hypertension the long IRP is probably the result of the increased aortic pressure in most patients since mean ΔIRP is normal in some patients there may also be a change in LV chamber compliance due to ventricular hypertrophy Systemic blood pre-

Table III Echocardiographic measurements in patients with coronary artery disease

HR beats/min	*True IRP msec*	*DE time msec*	*A E point msec*	*EF slope mm/sec*	*PR–AC msec*	*ICT msec*	*LVDd cm*	*LVDs cm*	*% ΔS*	*Ao closing pressure mm Hg*
a According to systolic shortening fraction										
Group 1 (% ΔS > 25%) n = 6 75 ± 12	85 ± 10	65 ± 15	150 ± 20	84 ± 31	65 ± 7	37 ± 28	5.3 ± 0.5	3.4 ± 0.5	36 ± 6	113 ± 6
Group 2 (% ΔS ≤ 25%) n = 9 94 ± 10	59 ± 30	56 ± 23	114 ± 37	117 ± 4?	36 ± 22	35 ± 15	6.3 ± 0.8	5.3 ± 0.9	17 ± 7	118 ± 16
b According to duration of IRP										
Group 1 (Short IRP) n = 4 108 ± 8	33 ± 22	58 ± 22	90 ± 2?	114 ± 52	46 ± 7	45 ± ?	6.3 ± 0.6	5.0 ± 0.6	21 ± 6	108 ± 5
Group 2 (Normal IRP) n = 1 87	60	50	110	143	?0	—	8.0	6.9	14	133
Group 3 (Prolonged IRP) n = 10 81 ± 12	85 ± 10	61 ± 21	146 ± 28	96 ± 37	41 ± 22	30 ± 22	5.6 ± 0.4	4.1 ± 1.1	27 ± 12	116 ± 13

See text for details of indices and abbreviations
$p < 0.05$, $p < 0.01$, $p < 0.001$ } Compared to the normal group

an over all linear relationship between IRP and A–E ($r = 0.87$ $p < 0.001$)

Other echocardiographic measurements related to LV compliance The *mitral EF slope* was decreased in hypertension ($p < 0.001$) aortic stenosis ($p < 0.05$) and aortic incompetence ($p < 0.01$) and was greatly decreased in HOCM ($p < 0.001$) It was also decreased ($p < 0.05$) in the six patients with CAD who had normal LV function (% ΔS > 25%) but was not different from normal when the whole CAD group was examined together The EF slope tended to increase in CMO although the difference was not statistically significant The inverse relation between IRP and the mitral EF slope in different diseases is shown in Fig 4*A* Diseases associated with a prolonged IRP had a reduced mitral EF slope in CMO IRP was short and the EF slope increased In MS both IRP and the mitral EF slope were very short The relation between IRP and EF slope tended to be positive however within the group of normal subjects (Fig 4*B*) and was positive or unrelated within the other disease states

The *PR AC time* was 70 ± 7 msec in normal subjects It was normal in AS AI and HOCM and slightly decreased in hypertension (ns) The PR–AC time was short in the nine patients with CAD who had a decreased shortening fraction ($p < 0.001$) There was no relation between the PR–AC time and IRP

Relation between IRP and measurements of systolic LV performance

1 Isovolumic contraction time ICT was 38 ± 22 msec in normal subjects it was shortened in AI and MS and increased in CMO the differences did not reach statistical significance because the number of patients in which the measurement could be made accurately was small The mean values for ICT and IRP in

Other simple echocardiographic measurements which have been related to LV compliance include the mitral EF slope and the PR–AC time The mitral EF slope is related to early diastolic filling and in the absence of mitral stenosis to early diastolic compliance [3] IRP and the A–E point time measure a similar phenomenon to the EF slope—the rate of LV relaxation and filling in early diastole—and were related to the mitral EF slope The three measurements do not examine precisely the same period in diastole however studies of LV relaxation and compliance should define very carefully the exact period of diastole to which they refer since the diastolic pressure volume and stress strain relations change throughout diastole [4] The PR AC time is a very rough and not constant measurement of end-diastolic compliance a long AC time (short PR AC) indicating a high LV end diastolic pressure [7] there was no relation between the PR AC time and true IRP which measures LV function in early diastole

There was a positive relationship between systolic LV shortening (% ΔS) and the duration of the IRP in different cardiac diseases In HOCM % ΔS was increased and IRP greatly prolonged while in CMO % ΔS was reduced and IRP was short Patients with increased contractility may have an increased intracellular Ca and this may prolong early diastolic relaxation an active process dependent on the Ca reuptake mechanisms increased systolic tension may therefore be associated with greater residual tension during early diastole and a prolonged IRP We did not make serial studies of the effects of positive and negative inotropic intervention in the same patients however and can provide no further information relating to these changes Similarly the relationship between ICT and IRP was not clear in our study although hemodynamic studies have shown that peak negative dp/dt is related to peak positive dp/dt

Summary

Isovolumic relaxation period (IRP) was measured noninvasively from the onset of the aortic component of the second heart sound on the phonocardiogram to the point of separation of the mitral leaflets on the echocardiogram IRP was measured in 83 patients 10 normal subjects and 73 patients with different cardiac diseases The duration of IRP was 58 ± 11 msec in normal subjects It was prolonged in hypertension ($p < 0.001$) HOCM ($p < 0.001$) aortic stenosis ($p < 0.05$) and aortic incompetence ($p < 0.01$), and was shortened in congestive cardiomyopathy ($p < 0.05$) and mitral stenosis ($p < 0.01$) In patients with coronary artery disease and normal overall systolic LV function IRP was prolonged ($p < 0.001$) IRP was shortened in four patients with coronary disease who had severe LV dysfunction and severe additional mitral incompetence

IRP was related to systemic blood pressure percentage shortening of the LV in systole and to the mitral EF slope It tended to increase with increasing heart rate and a regression equation was developed for predicting IRP in relation to blood pressure and heart rate in normal subjects There was no relation to the PR AC time or to isovolumic contraction time IRP is a useful measurement of LV dynamics in early diastole

REFERENCES

1 Grossman W, and Tift Mann J Evidence for impaired myocardial relaxation during acute ischaemia in man Fourth Workshop on Contractile Behaviour of the Heart Eur J Cardiol 7(Suppl) 239 1978
2 Rickards, A and Seabra Gromes, R Changes in regional diastolic function of the left ventricle following the induction of angina Fourth Workshop on Contractile Behaviour of the Heart Eur J Cardiol 7(Suppl) [illegible] 1978
3 Gibson D G Prewitt T A, and Brown D J Analysis of left ventricular wall movement during isovolumic relaxation and its relation to coronary artery disease Br Heart J 38 1010 1976
4 Upton M T and Gibson D G The study of left ventricular function from digitised echocardiograms Progr Cardiovasc Dis 10 359 1978
5 Lewis, B S and Gotsman M S Current concepts of left ventricular relaxation and compliance Am Heart J 99 101 1980
6 Arevalo F and Sakamoto T On the duration of the isovolumetric relaxation period (IVRP) in dog and man Am Heart J 67 651 1964
7 Kumar S and Spodick D H Study of the mechanical events of the left ventricle by atraumatic techniques comparison of methods of measurement and their significance Am Heart J 80 401 1970
8 Rubenstein J J Pohost G M Dinsmore R E and Harthorne J W The echocardiographic determination of mitral valve opening and closure Correlation with hemodynamic studies in man Circulation 51 [illegible] 1975
9 D Angelo R Shah, N, and Rubler S Diastolic time intervals in ischemic and hypertensive heart disease comparison of isovolumic relaxation time and rapid filling time with systolic time intervals Chest 68 [illegible] 1975

sure and heart rate are easy to measure at the bedside however and can be taken into account when assessing measurements of IRP in different cardiac diseases

IRP is prolonged in most patients with coronary artery disease especially in those in whom over all LV contraction as measured by % ΔS is normal IRP was prolonged in all but one patient but mean ΔIRP was essentially normal since one patient in the group had a very low ΔIRP (−48 msec) These data confirm previous studies[9, 17] and probably correspond to the decreased peak negative dp/dt in patients with myocardial ischemia[1] The increased IRP may also be related to asynchronous relaxation of different regions of the myocardium[3] (Fig 7) It is interesting that patients with severe extensive LV dysfunction and functional mitral incompetence have a short IRP Mean ΔIRP was again almost normal since one patient had a prolonged corrected IRP but ΔIRP was short in the other patients in the subset confirming a real shortening of the duration of isovolumic relaxation The findings in these patients are similar to those of congestive cardiomyopathy where the large dilated left ventricle may have increased operative chamber compliance at operative volume in early diastole The rapid mitral EF slope supports this concept although a high LA pressure and high LA v wave may contribute to the shortened IRP *in patients with severe LV dysfunction and* important functional mitral incompetence

Aortic incompetence was associated with a prolonged IRP and ΔIRP There is no true isovolumic relaxation period in aortic incompetence and ventricular filling commences immediately with *the onset* of ventricular *relaxation* retrograde ventricular fillig may delay the onset of mitral valve opening although there may also be a decrease in LV chamber compliance because of ventricular hypertrophy and volume overload which further prolongs measured IRP

The DE time was normal in all groups of patients except those with HOCM who had a prolonged DE time and the A_2–E point time which increased *in general in parallel* with the increase in true IRP was longest in patients with HOCM The great increase in DE time in HOCM may be related to the severe LVH and decreased chamber compliance which occurs in severe LV hypertrophy It is noteworthy that the DE time was not prolonged in hypertension emphasizing

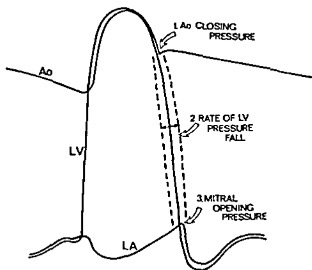


Fig 7 Diagrammatic left ventricular *(LV)* aortic *(Ao)* and left atrial *(LA)* pressure pulse tracings Isovolumic relaxation period (IRP) depends on (1) aortic closing pressure (2) rate of fall of LV pressure and (3) mitral opening pressure The rate of fall of LV pressure may be the resultant of regional asynchrony in ventricular relaxation in patients with cardiac diseases

again the importance of the high aortic pressure rather than the LV hypertrophy in the prolongation of IRP in hypertensive patients The mean DE time was also not prolonged in coronary artery disease It seems that changes in regional muscle stiffness due to fibrosis (CAD) or mild *to moderate LVH and moderate changes in LV* chamber stiffness (hypertension AS) are not sufficient to affect mitral valve opening once this has started it is only in patients with severely abnormal chamber stiffness due to unusual LV hypertrophy and geometrical changes within the *ventricle (e g HOCM) that there is prolongation* of the mitral valve opening time DE

The study also provides information in relation to the A_2–E point (A –OS time) in normal subjects and in patients with mitral stenosis[6, 2] Measurement of true IRP is a better measurement of the severity of MS than total time A_2–OS since mitral valve thickening and rigidity may prolong the DE time in some patients with severe MS to offset the extreme *shortening of true* IRP in patients with severe disease The normal A –E point time is 116 ± 13 msec There is a decrease in A –OS time in MS but we did not subdivide patients with MS further since not all patients with mitral stenosis underwent cardiac catheterization

The relationship of pulmonary artery wedge pressure to the posterior aortic wall echocardiogram in patients free of obstructive mitral valve disease

Alan G Wasserman, M D
Jerry F Meyer M D F A C C
Allan M Ross M D F A C C
Washington D C

Numerous investigations have been designed to uncover reliable echocardiographic measurements which reflect human left ventricular compliance Since decreased left ventricular compliance will be reflected in an increased left ventricular filling or pulmonary artery wedge pressure a noninvasive method to assess this pressure would have widespread clinical utility

Based upon echocardiographic measurements it has been proposed that characteristic aortic wall motion represents left atrial filling and emptying events [3] Resistance to left atrial emptying was estimated by Strunk and colleagues using the fraction of passive posterior aortic wall motion occurring in the first third of diastole (atrial emptying index AEI) In that study patients had fixed mitral valve obstruction as the cause of prolonged left atrial emptying

The purpose of this study was to evaluate the relationship of this index (AEI) to left ventricular filling pressures in patients free of mitral valve obstruction which in such patients is primarily related to differences in left ventricular compliance

Materials and methods

Twenty five consecutive unselected patients requiring hemodynamic evaluation had M mode echocardiography performed at the time of left ventricular filling pressure (pulmonary capillary wedge) measurement Data from six patients were rejected four because of suboptimal echocardiograms and two because of evidence of mitral stenosis Two patients were studied twice, one after a change in heart rhythm and the other after treatment with vasodilators for a total of 21 studies in 19 patients Studies were performed after informed consent was obtained There were eight women and 11 men with a mean age of 53 years (range 30 to 74 years) The final diagnosis was coronary artery disease in 14 patients, congestive cardiomyopathy in two and three patients were judged to be normal

Echocardiograms were made using a 2.25 MHz transducer placed along the left sternal border in the third or fourth intercostal space and rotated until elements of aortic leaflets were seen within the aortic root The image of the aortic root was expanded to the maximum recording scale in order to facilitate measurements All aortic measurements were made in that part of the recording showing maximal total aortic root excursion

The method described by Strunk and associates[4] and by Lewis and colleagues[3] for determining the atrial emptying index was employed For patients in sinus rhythm posterior aortic wall motion reflecting passive left ventricular filling is from points O to A (Fig 1) The point where the posterior aortic wall begins its posterior motion is O and the A point describes a second abrupt posterior movement caused by atrial contraction. The left atrial emptying index (X/OA) is the ratio of the posterior aortic wall motion occurring in

From the Division of Card l gy L epartment of Medicine The George Washington University Med al Center Washington D C

Received for publication J 9 9

Accepted for publication No 9 9

Reprint requests Alan G Wa M D The George Washington University Medical Center 21 nsylvania Ave N W Washington, D C 20037

0002 8703/80/100500 + 06$00 00/0 © 1980 The C V Mosby Co

10 Popp R L, Filly K Brown O R and Harrison D C Effect of transducer placement on echocardiographic measurement of left ventricular dimensions Am J Cardiol 35 537 19 5

11 Upton M T Gibson D G and Brown D J Instantaneous mitral valve leaflet velocity and its relation to left ventricular wall movement in normal subjects Br Heart J 38 51 1976

12 Konecke L L Feigenbaum H Chang S Corya B and Fischer J C Abnormal mitral valve motion in patients with elevated left ventricular diastolic pressures Circulation 47 989 1973

13 Gibson D G Traill T A and Brown D J Left ventricular wall thickness changes in normal subjects and patients with ischaemic heart disease Br Heart J 39 340 1977

14 Bechimol A, and Ellis J G A study of the period of isovolumic relaxation in normal subjects and in patients with heart disease Am J Cardiol 19 196 196

15 Harmjanz D Bottcher D and Schertlein G Correlation of electrocardiographic pattern shape of ventricular septum and isovolumetric relaxation time in irregular hypertrophic cardiomyopathy (obstructive cardiopathy) Br Heart J 33 9 8 1971

16 Kimura Y Matsuo H Mochizuki S, Aoki, K Wada O and Abe H Analysis of a cardiac cycle of the left side of the heart in cases of left ventricular overloading or damage with the ultrasonic Doppler method AM HEART J 75 49 1968

17 Rubenstein J J Pohost G M, Foster J R and Sanders C A The echocardiographic determination of isovolumic relaxation period in patients with normal and diseased coronary arteries Clin Res 21 446 1973

18 Rubenstein J J Pohost G M Dinsmore R E and Harthorne J W The echocardiographic determination of mitral valve opening and closure Correlation with hemodynamic studies in man Circulation 51 98 19 5

19 Brodie B R Grossman W McLaurin L Starek P J K and Craige E Diagnosis of prosthetic mitral valve malfunction with combined echo phonocardiography Circulation 53 93 1976

20 Grossman W McLaurin L P Moos, S P, Stefadouros, M and Young D T Wall thickness and diastolic properties of the left ventricle Circulation 49 129 1974

21 Gaasch, W H Levine H J Quinones M A and Alexander J K Left ventricular compliance mechanisms and clinical implications Am J Cardiol 38 645 1976

22 Kalmanson D Veyrat C Bernier A, Witchitz S and Chiche P Opening snap and isovolumic relaxation period in relation to mitral valve flow in patients with mitral stenosis Significance of A OS interval Br Heart J 38 135 19 6

23 DeMaria A N, Miller R R Amsterdam E A, Markson, W, and Mason D T Mitral valve early diastolic closing velocity in the echocardiogram relation to sequential diastolic flow and ventricular compliance Am J Cardiol 37 693 19 6

24 Gibson D G and Brown D J Relation between diastolic left ventricular wall stress and strain in man Br Heart J 36 1066 1974

25 Rankin J S Arentzen C E, McHale P A Ling D, and Anderson R W Viscoelastic properties of the diastolic left ventricle in the conscious dog Circ Res 41 37 1977

26 Moskowitz, S E Lewis B S Halon D A Amar R, and Gotsman M S Computer prediction of left ventricular compliance throughout diastole in normal patients Fourth Workshop on Contractile Behaviour of the Heart Eur J Cardiol 7(Suppl) 171 19 8

27 Lewis J R Parker J O and Burggraf G W Mitral valve motion and changes in left ventricular end diastolic pressure a correlative study of the PR AC interval Am J Cardiol 42 383 19 8

28 Cohn P F Liedtke A J Serur J, Sonnenblick E H, and Urschel C W Maximal rate of pressure fall (peak negative dP/dt) during ventricular relaxation Cardiovasc Res 6 263 19 2

29 Lewis B S and Gotsman M S Maximal rate of fall of left ventricular pressure in cardiomyopathy and constrictive pericarditis S Afr Med J 49 1287 19 5

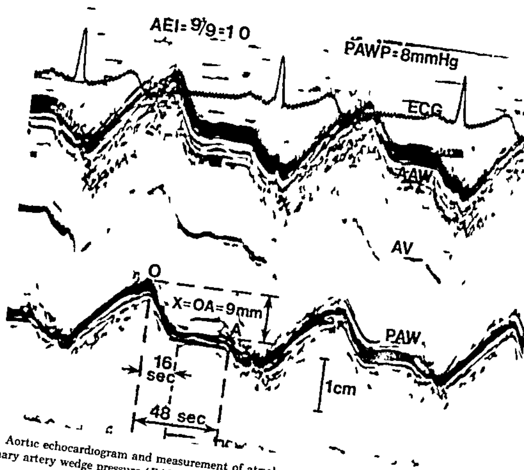


Fig 2 Aortic echocardiogram and measurement of atrial emptying index (*AEI*) from a patient with a nor
pulmonary artery wedge pressure (*PAWP*) Abbreviations same as in *Fig 1*

Table I Summary of data

Case No	*Age (yr)*	*Sex*	*Diagnosis*	*Rate rhythm*	*TAE (mm)*	*AEI*	*PAWP (m*
Group A (PAWP ≤ 12 mm Hg)							
1	45	M	CAD	107 S	7 1	0 88	8
2	74	F	CAD	60 J	6 0	1 00	9
3	64	M	CAD	60 S	7 6	0 8?	5
4	62	M	CAD	67 S	10 5	1 00	5
5	54	M	CAD	68 S	9 0	0 93	9
6	54	M	CAD	78 S	9 0	1 00	7
7	30	M	N	79 S	11 2	1 00	8
8	42	M	CAD	73 S	10 7	0 91	4
9	47	M	N	80 S	10 0	0 88	6
10	51	F	CAD	65 S	10 8	1 00	8
11	42	F	N	77 S	9 1	0 90	6
12	53	M	CAD	74 S	10 7	0 93	8
Group B (PAWP > 12 mm Hg)							
1	[illegible]	M	CM	102 S	5 0	0 63	22
2	51	F	CAD	72 S	6 4	0 64	25
3	44	F	CM	115 J	8 9	0 43	[illegible]
4	44	F	CM	91 S	10 0	0 40	27
5	58	F	CAD	101 S	3 5	0 36	35
6	64	F	CAD	83 AF	8 1	0 56	22
7	70	F	CAD	81 S	4 0	1 00	15
8	54	M	CAD	[illegible] AF	4.2	0 66	19
9	54	M	CAD	72 AF	4 0	0 78	15

Abbreviations AEI = atrial emptying index AF = atrial fibrillation CAD = coronary artery disease CM = cardiomyopathy J = junctional rhythm N = normal PAWP = pulmonary artery wedge pressure S = sinus rhythm TAE = total aortic excursion

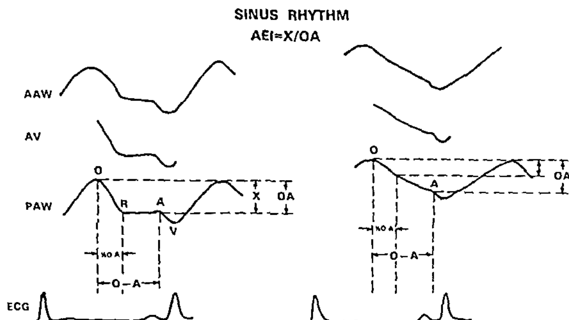


Fig 1 Schematic drawing illustrating the calculation of the atrial emptying index (*AEI*) for patients in sinus rhythm *Left* AEI = X/OA ≈ 1 0 *Right* AEI = X/OA < 1 0 I assive atrial emptying occurs between points *O* and *A* Abbreviations *AAW* = anterior aortic wall *AV* = aortic valve *PAW* = posterior aortic wall

the first third of this passive emptying period (X) to the total passive emptying (OA) For patients in atrial fibrillation the end of the passive dias tole is taken as the onset of ventricular systole Point V on the posterior aortic wall echocardio gram corresponds to the end of the QRS complex on the electrocardiogram The atrial emptying index is again the ratio of the motion occurring during the first third of this period (X) to the total passive emptying (OV)

The anterior posterior excursion of the aortic root was measured using only the leading edge of the posterior aortic wall echo and averaged over five cycles Linear regression equations and corre lation coefficients were calculated and group comparisons were made using Student s unpaired t test

Results

There were 12 patients with normal hemody namics (group A filling pressure ≤ 12 mm Hg), and seven patients (nine studies) with abnormal hemodynamics (group B filling pressure > 12 mm Hg) (Table I) Of the 12 patients in group A 11 were in sinus rhythm and one in a junctional rhythm For group B four were in sinus rhythm two in atrial fibrillation (one studied twice) and one patient was studied first in a junctional rhythm and then after conversion to sinus rhythm The mean pulmonary wedge pressures for groups A and B were 6 9 ± 1 7 mm Hg (mean ± S D) and 23 6 ± 6 9 mm Hg respec tively ($p < 0 01$)

Figs 2 and 3 demonstrate normal and abnor mal AEI s respectively The mean atrial empty ing index for Group A was 0 94 ± 0 06 and for group B it was 0 61 ± 0 02 ($p < 0 001$) (Fig 4) There was a significant ($p < 0 001$) negative cor relation between pulmonary artery wedge pres sure and the AEI r = −0 91 Mean heart rate for group A was 74 beats/minute compared to 89 beats/minute in group B ($p < 0 05$) Because of the potential influence of heart rate on the left atrial emptying pattern and because of the differ ences in heart rate in our two groups we investi gated the possibility that the differences observed in the AEI were secondary only to rate Normal ization for heart rate was accomplished by divid ing the AEI by $\sqrt{RR}$ A significant ($p < 0 001$) correlation remained with an r value of −0 85 (Fig 5)

No patient in the normal group had an atrial emptying index below 0 80 and no patient in group B with a pulmonary wedge pressure greater

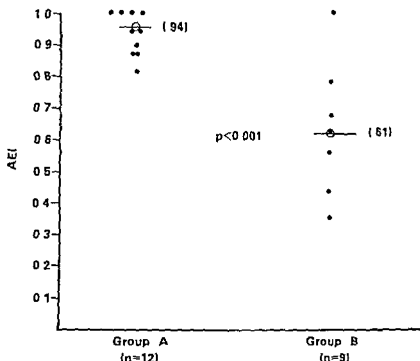


Fig 4 The atrial emptying index (*AEI*) in patients with normal (group A PAWP ≤ 12 mm Hg) and abnormal (group B PAWP > 12 mm Hg) pulmonary artery wedge pressures *P* = probability

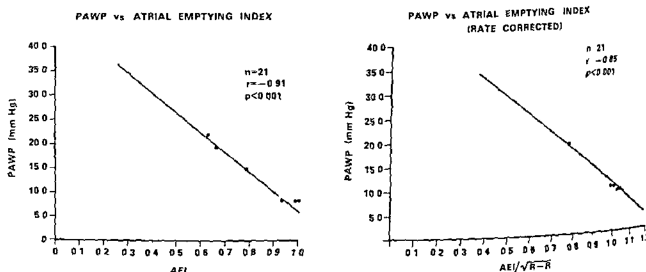


Fig 5 Pulmonary artery wedge pressure (*PAWP*) plotted against the atrial emptying index (*AEI*) *Left* before and *right* after rate correction There is a high degree of negative correlation both before (r = -0 91) and after (r = -0 85) rate correction p = probability

root excursion in patients with valvular heart disease and found a statistically significant decrease in motion in patients with mitral stenosis and a statistically significant increase in motion in patients with mitral regurgitation as compared to a normal population They found no significant difference in patients with aortic regurgitation as compared to the normal population We did not include data from patients wit significant valvular disease but recognize th possibility that markedly increased aortic com pliance or altered left atrial filling and emptyr secondary to severe mitral regurgitation ma alter these correlations

Total anteroposterior aortic root motion c total aortic root excursion (TAE) has correlate

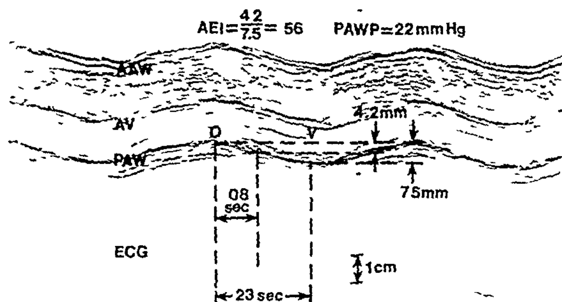


Fig 3 Aortic echocardiogram and measurement of atrial emptying index (AEI) from a patient with an elevated pulmonary artery wedge pressure (PAWP) Abbreviations same as in Fig 1

than 18 mm Hg had an atrial emptying index greater than 0.66

The total aortic root excursion for groups A and B were 9.2 ± 1.9 mm and 6.0 ± 2.4 mm ($p < 0.01$) respectively. When the total aortic root excursion was related to the pulmonary wedge pressure for the total population there was a very weak correlation with an r value of −0.46 ($p < 0.04$) which did not improve after normalizing for rate

Discussion

Previous attempts to establish echocardiographic determinants of left ventricular pressure and compliance have concentrated on the mitral valve echocardiogram. Konecke and co workers[6] reported that the echocardiographic pattern of mitral valve motion is altered in patients with markedly elevated left ventricular diastolic pressure. They found that a PR AC interval of 0.06 sec or less as derived from the electrocardiogram and mitral valve echocardiogram correlated with an elevated left ventricular end diastolic pressure (≥ 20 mm Hg) when the atrial component of the left ventricular pressure pulse is at least 8 mm Hg. A recent report by Lewis and co workers did not substantiate the reliability of this measurement either in the resting or the dynamic state

It has been suggested that the mitral E F slope may be a function of left ventricular compliance.[7,8] A decrease in the diastolic closure rate of the mitral valve a constant finding in mitral stenosis has also been reported in conditions without mitral valve pathology but with impaired left ventricular filling. DeMaria and co workers established a correlation between transmitral flow in the first third of diastole and the E F slope ($r = 0.87$) and although the mitral E F slope did not correlate closely with compliance they found that ventricular compliance was generally reduced in patients with an early mitral diastolic closing velocity of less than 75 mm/second. Vignola and associates[9] demonstrated that the pressure/volume relationship in the left ventricle in early diastole is an important determinant of the mitral E F slope

Although the echocardiographically observed aortic root motion may be the result of many factors including aortic compliance, Strunk and co workers and Akgun and colleagues presented data supporting the hypothesis that aortic wall motion is governed mainly by the rate of left atrial volume changes. The posteriorly directed aortic wall motion during ventricular diastole would then be secondary to the rate of left atrial emptying. Mechanical obstruction to flow of blood at the level of the mitral valve alters the pattern of left atrial emptying and Strunk and co workers[4] quantified the degree of obstruction with the echocardiographically measured atrial emptying index

Akgun and associates[11] also compared aortic

Ischemic cardiomyopathy: A clinicopathologic study of fourteen patients

Edward H. Schuster, M.D.
Bernadine H. Bulkley, M.D.
Baltimore, Md.

A cardiomyopathy due to coronary artery disease is a relatively new concept first proposed in 1969.[1] In 1970 Burch and co-workers[2] coined the term "ischemic cardiomyopathy" for those patients with coronary artery disease, enlarged hearts, and the clinical manifestations of a congestive cardiomyopathy. Since that time, further information has been obtained from natural history[3, 4] and cardiac catheterization[5] studies of patients with ischemic cardiomyopathy. The term "ischemic cardiomyopathy" has been broadened by some to include any patient with coronary disease and a decreased left ventricular ejection fraction regardless of symptoms or heart size.[3] In order to define a morphological explanation for ischemic cardiomyopathy, we studied 14 autopsied patients who met the clinical criteria for ischemic cardiomyopathy. At autopsy these patients had severe coronary artery disease with injury in multiple vascular distributions. Although the hearts were dilated and hypertrophied, the myocardial walls were disproportionately thinned, suggesting inadequate myocardial thickness for the degree of dilatation. The latter may be a factor contributing to the diffuse inadequacy of myocardial function in a disease of regional injury.

Materials and methods

Patients from the autopsy files of The Johns Hopkins Hospital were included in this study if they met the clinical definition of this entity[4] including significant (> 75%) coronary narrowing in at least one vessel, a longstanding clinical history of congestive heart failure, cardiomegaly, and if the hearts had been routinely processed at autopsy with postmortem coronary arteriography and fixation of the heart in formalin in an intact distended state. Patients were excluded if (1) there was a history of hypertension or alcohol abuse, (2) there was evidence of primary valvular disease, congenital heart disease, or ventricular aneurysm formation, or (3) there was evidence of other etiologies of cardiomyopathy (sarcoid, amyloid, hypertrophic cardiomyopathy, etc.). Over 200 consecutive autopsy cases with coronary artery disease whose hearts had been similarly processed at autopsy were reviewed and 14 met the above clinical criteria for inclusion in this study. The patient's clinical records were studied and coronary risk factors, electrocardiograms, and chest radiographics were reviewed and tabulated.

At autopsy, all hearts were prepared by postmortem angiography utilizing injection of a gelatin pigment barium mass at pressures of 100 to 150 mm Hg controlled by manometer and subsequently fixed in formalin in a distended state. Sets of stereoscopic radiographs were prepared of the intact heart and its transverse sections. The hearts were studied grossly and histologically for the presence of myocardial lesions and obstructive disease of the coronary arteries. The hearts were serially sliced and transverse sections were subjected to planimetry denoting areas of remote and recent myocardial necrosis. Each transverse slice was weighed minus the right ventricle. Using a digitizing computer (Hewlett Packard), the grams of infarcted tissue and the percent of left ventricle infarcted was obtained.

From the Departments of Medicine and Pathology of The Johns Hopkins Hospital, Baltimo

Supported in part by Grant No. 5 P50-HL-1 6?5 Specialized Center of Research and the Peter Belfer Laboratory for Myocardial Research.

Received for publication June ?8, 1979.

Accepted for publication Sept. 14, 1979.

Reprint requests: Bernadine H. Bulkley, M.D., The Johns Hopkins Hospital, 600 N. Wolfe St., Baltimore, Md. ?120?

0002-8703/80/100?06 + 0?$00.?0/0 © 1980 The C. V. Mosby Co.

with stroke volume or stroke index [13,14] but has not been characterized as a function of left ventricular diastolic hemodynamics Burggraf and colleagues [2] looking at total aortic root systolic anteroposterior motion found that a value < 7 mm indicated poor left ventricular performance although they did not find it to be a predictor of abnormal left ventricular end diastolic pressure We found only a very weak correlation between total aortic root excursion and mean pulmonary artery wedge pressure but the mean total excursion for those patients with pulmonary wedge pressures > 12 mm Hg was 6 0 ± 2 4 mm Although there was considerable overlap of values this was significantly ($p < 0.01$) lower than those patients with wedge pressures ≤ 12 mm Hg whose excursion was 9 2 ± 1 9 mm

The results of this study indicate that the atrial emptying index provides a noninvasive measure of left ventricular filling pressures in a diverse group of patients This relationship is not limited to patients with obstructive mitral valve disease and therefore may have more general clinical utility

Summary

Aortic wall echocardiograms were obtained simultaneously with pulmonary artery wedge pressures (PAWP) in 21 patients free of obstructive mitral valve disease There was a significant ($p < 0.001$) negative correlation between the fraction of passive posterior aortic wall motion occurring in the first third of diastole (the atrial emptying index—AEI) and the pulmonary artery wedge pressure ($r = -0.91$) The AEI for patients with normal PAWP (≤ 12 mm Hg) was 0 94 ± 0 06 (mean ± S D) compared with 0 61 ± 0 20 for those with abnormal PAWP (> 12 mm Hg) No patient with a normal PAWP had an AEI < 0 80 and no patient with a PAWP > 18 mm Hg had an AEI > 0 66 These data suggest that analogous to the reported use of the AEI to estimate severity of mitral obstruction the index provides a noninvasive measure of left ventricular filling pressure when the mitral valve is normal

We gratefully acknowledge the technical assistance of Daniel Bogoty and the secretarial assistance of Peggy Deese and Barbara Bragg in the preparation of this manuscript

REFERENCES

1 Strunk B L Fitzgerald J W Lipton M Popp R L and Barry W H The posterior aortic wall echocardiogram Its relationship to left atrial volume change Circulation 54 744 1976
2 Burggraf G W Mathew T, and Parker J O Aortic root motion determined by ultrasound Relation to cardiac performance in man Cathet Cardiovasc Diagn 4 29 1978
3 Shah P M, and Sylvester L J Echocardiography of the aortic and pulmonary valves, Progr Cardiovasc Dis 20 451 1978
4 Strunk, B L London E J, Fitzgerald J, Popp R L, and Barry W H The assessment of mitral stenosis and prosthetic mitral valve obstruction using the posterior aortic wall echocardiogram Circulation 55 885 1977
5 Lewis J R Parker J O and Burggraf G W Mitral valve motion and changes in left ventricular end diastolic pressure A correlative study of the PR AC interval Am J Cardiol 42 383, 1978
6 Konecke L L, Feigenbaum H, Chang S Corya, B C, and Fischer J C Abnormal mitral valve motion in patients with elevated left ventricular diastolic pressures Circulation 47 989 1973
7 Bergeron G A, Cohen M V Teichholz, L E, and Gorlin R Echocardiographic analysis of mitral valve motion after acute myocardial infarction Circulation 51 8? 1975
8 Quinones, M A Gaasch W H, Waisser E, and Alexander J K Reduction in the rate of diastolic descent of the mitral valve echogram in patients with altered left ventricular diastolic pressure-volume relation Circulation 49 246 1974
9 DeMaria A N, Miller R R, Amsterdam E A, Markson W and Mason D T Mitral valve early diastolic closing velocity in the echocardiogram Relation to sequential diastolic flow and ventricular compliance Am J Cardiol 37 693 1976
10 Schattenberg T T Echocardiographic diagnosis of left atrial myxoma Mayo Clin Proc. 43 6?0 1968
11 Layton C, Gent G, Pridie R, McDonald A, and Brigden W Diastolic closure rate of normal mitral valve Br Heart J 35 1066 1973
12 Vignola P A, Walker H J Gold H K and Leinbach R C Alteration of the left ventricular pressure-volume relationship in man and its effect on the mitral echocardiographic early diastolic closure slope Circulation 566 586 1977
13 Akgun G, and Layton C Aortic root and left atrial wall motion An echocardiographic study Br Heart J 39 108? 1977
14 Pratt R C, Parisi, A F Harrington J J and Sasahara A A The influence of left ventricular stroke volume on aortic root motion Circulation 53 947 1976

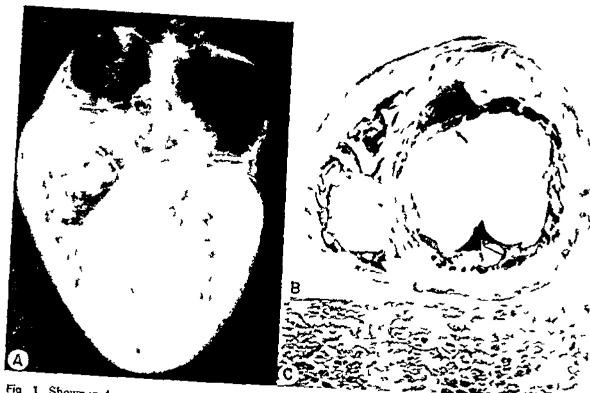


Fig 1 Shown in *A* is a postmortem angiogram of a patient with ischemic cardiomyopathy The heart is diffusely dilated the walls are thinned and severe coronary occlusive disease is present A transverse section through both right and left ventricles is shown in *B* Subendocardial infarcts are present anteriorly laterally posteriorly and a transmural infarct is present in the septum A mural thrombus overlays the anteroseptal infarct (arrow) All infarcts were healed (*C*) showing well formed fibrous tissue (Hematoxylin and eosin original magnification ×200)

measured only at points without gross and histological evidence of necrosis or fibrosis were as follows anterior 1 2 cm ± 0 1 lateral 1 1 cm ± 0 1 posterior 1 1 cm ± 0 2 and septal 1 1 cm ± 0 1 These wall thickness measurements were compared with those of patients who died from recurrent infarctions without a clinical diagnosis of ischemic cardiomyopathy (Table III) and with those of patients with primary valvular insufficiency and primary myocardial disease The mean anterior posterior lateral and septal wall thickness as well as the total average wall thickness for the group with ischemic cardiomyopathy was significantly thinner than the wall thickness of patients with recurrent infarctions valvular insufficiency or primary myocardial disease ($p < 0\ 01$ unpaired t test)

Examination of the coronary tree in the 14 patients with ischemic cardiomyopathy revealed multiple vessel involvement by atherosclerosis in all patients In sev r patients three major vessels were narrowed 7 nd in seven patients two vessel involvement was present (average 2.5 major coronary ar es) None of the patients had significant left main disease and all of the patients had well developed collaterals visible by postmortem angiogram (Fig 2) Of the 14 patients seven (50%) had infarcted or scarred papillary muscles and seven (50%) had mural thrombi By gross and histological evaluation one patient had only one remote myocardial infarction but one which involved 50% of the left ventricular circumference Seven had two infarcts four had three infarcts and two had four infarcts all involving at least two vascular distributions Of the 14 patients 12 had anterior infarctions (four transmural eight subendocardial) nine had posterior infarctions (one transmural eight subendocardial) and eight had lateral infarctions (three transmural five subendocardial)

The amount of infarcted myocardium determined by planimetry ranged from 8% to 46% (average 25%) In only four patients (28%) was more than 30% of the left ventricle involved, and in four patients less than 20% of the myocardium was infarcted Histologic examination showed well formed myocardial scars in all hearts. In the

Table I Clinical findings

Number of patients	14
Age	40-81 (avg 62 yrs)
Sex	3 females (21%) 11 males (85%)
Diabetes	3 (21%)
Hypercholesterolemia	3 (21%)
Myocardial infarction	8 (64%)
Angina pectoris	6 (42%)
Congestive heart failure	14 (100%)
Electrocardiogram	
Remote myocardial infarction	5 (36%)
Acute myocardial infarction	2 (14%)
Conduction disturbances	7 (50%)
Atrial arrhythmias	3 (21%)
Ventricular arrhythmias	7 (50%)
Chest radiograph	
Cardiomegaly	14 (100%)
Increased pulmonary vascularity	3 (21%)
Pulmonary edema	6 (42%)

To compare ventricular wall thickness and over all topography 12 patients who died from recurrent myocardial infarctions 16 patients with chronic primary valvular insufficiency (eight mitral regurgitation eight aortic regurgitation) and 16 patients with primary congestive cardio myopathy were selected from the autopsy files

Results

Of over 200 cases studied 14 were identified which fulfilled the clinical criteria for ischemic cardiomyopathy

Clinical findings The clinical data of the 14 patients are summarized in Table I The patients ranged in age from 40 to 81 years (average 62 years) with 11 of 14 being male None of the patients had a history of hypertension or alcohol abuse Of the 14 patients three had diabetes mellitus (21%) and three had hypercholesterol emia (21%) Nine patients (64%) sustained a remote myocardial infarction by history six patients (42%) had angina pectoris and all 14 had longstanding symptoms of severe intractable congestive heart failure In none of the 14 patients were the electrocardiograms normal but in only half of the patients were the changes diagnostic for myocardial infarction The electro cardiogram revealed remote myocardial infarc tion in five patients (36%) and acute infarction in two (14%) Conduction disturbances were fre quent in these patients three (21%) had a left bundle branch block two (14%) a right bundle branch block and two had a left anterior hemiblock Three of the patients were in atrial fibrillation and three had recurrent episodes of ventricular tachycardia Cardiomegaly on chest radiograph was noted in all patients and nine patients (64%) had radiographic evidence of con gestive heart failure at their most recent exami nation

Table II Causes of death

	No of patients and %
Ventricular tachycardia/ventricular fibrillation	7 (50%)
Hypotension	2 (14%)
Acute myocardial infarction	1 (7%)
Intractable heart failure	4 (29%)

The immediate causes of death of the patients are shown in Table II Seven patients (50%) died suddenly of documented ventricular arrhythmias two (14%) from hypotension one from an acute myocardial infarction and four (28%) from intractable heart failure

Autopsy findings The average heart weight was 625 grams with a range of 450 to 830 grams. All the hearts had biventricular dilatation with no evidence of discrete aneurysm formation (Figs 1 and 2) Although the average total heart weight (625 grams) and the average left ventricular weight (290 grams) were above normal and indi cative of cardiac enlargement the maximal left ventricular wall thickness was not increased The average maximal left ventricular wall thickness



Fig 3 Shown here are a postmortem angiogram (*A*) and a gross specimen (*B*) of a heart with an anteroseptal aneurysm of the left ventricle Although the infarct is large and the coronary disease severe in contrast to ischemic myocardiopathy the heart here shows marked regional wall dilatation rather than a diffuse myocardiopathic type of dilatation. Thrombus is layered within the aneurysm (*arrows*)

tion[6] We have been able to identify only three reports describing autopsy findings in ischemic cardiomyopathy [3, 6, 11] and in only three patients were the studies detailed What distinguished the heart in ischemic cardiomyopathy from the heart of patients with prior infarctions and no evidence of left ventricular dysfunction remained unclear In this study of 14 autopsied patients with ischemic cardiomyopathy we examined several possible determinants of the diffuse left ventricular dysfunction including severity and extent of coronary disease total amount of left ventricle injured by old and new infarction heart size and wall thickness

As observed by others from clinical studies[1] a prominent feature of these patients was the severity of their coronary disease All had critical narrowings in at least two major coronary arteries and multiple lesions within at least one of these major vessels Half of the patients had > 75% narrowing in all three major vessels Severe coronary disease alone is not sufficient however to cause ischemic cardiomyopathy Most patients with coronary artery disease with and without infarction do not have congestive heart failure

All the hearts studied here with ischemic cardiomyopathy had grossly evident myocardial infarction Although one might surmise that the size of the infarction is a major determinant of ischemic cardiomyopathy as it has shown to be for cardiogenic shock[12] findings here suggest that the multiple sites of injury rather than the extent of the injury may be more important Our patients showed as little as 8% and as much as 46% of the left ventricle involved by infarction with an average of 25% infarction for the group Of the 14 patients four had less than 20% of their myocardium lost by old or new infarction In 13 of the 14 patients however infarcts were multiple

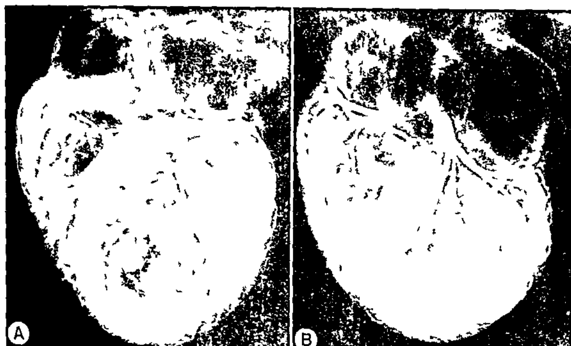


Fig 2 Postmortem angiogram from another patient with ischemic cardiomyopathy (*A*) again showing a globular diffusely dilated heart that has a similar shape to the heart in primary dilated cardiomyopathy an example of which is shown in *B* The coronary arteries in *A* are severely diseased but in *B* they are normal.

there was evidence of recent infarction as well but in each the recent infarcts were small involving less than 10% of the left ventricular wall The non infarcted myocardium histologically revealed focal myocardial cell hypertrophy foci of interstitial and perivascular fibrosis but no other evident or characteristic abnormality

Discussion

In 1969 Raftery and associates[1] reported four patients with a congestive cardiomyopathy who at catheterization had severe three vessel coronary artery disease They concluded that chronic ischemic heart disease could present as a cardiomyopathy and that before a diagnosis of primary congestive cardiomyopathy is made occlusive coronary disease must be excluded In 1970 Burch and colleagues[2] coined the term ischemic cardiomyopathy for those patients with coronary artery disease and severe ventricular dysfunction Two autopsied patients were studied who had focal fibrosis ventricular hypertrophy and ventricular dilatation Dash and co workers[3] presented their findings of 30 patients who had congestive heart failure and at cardiac catheterization had coronary artery disease decreased left ventricular ejection fraction (< 0 48) and widespread left ventricular wall motion abnormalities

In this study 14 autopsied patients with ischemic cardiomyopathy were studied Clinically all patients had heart failure with cardiomegaly and none had a history of hypertension or chronic alcoholism Although all patients had pathologic evidence of severe coronary artery disease and infarction only 64% had a history of myocardial infarction and only 42% had angina pectoris Two patients (14%) did not have a history of angina pectoris or myocardial infarction Furthermore in three patients the presence of bundle branch block on the electrocardiogram and the lack of a clear cut history of myocardial infarction led to a clinical diagnosis of primary myocardial disease One of the most striking electrocardiographic abnormalities in these patients was the frequency of ventricular dysrhythmias Eight patients had a history of recurrent ventricular ectopic beats and three had prior documented ventricular tachycardia or ventricular fibrillation

These clinical features of ischemic cardiomyopathy are compatible with the reports of others[1-4] What has received little attention however are the pathologic features of the heart in this condi

hypertrophy is a reflection of the intrinsic idiopathic myocardiopathic process in ischemic cardiomyopathy it seems likely that the severity of coronary disease and the limitations in blood supply combined with multifocal myocardial scarring limit the ability of the wall to respond appropriately to the demands of increased wall tension secondary to cavity dilatation

Summary

Ischemic cardiomyopathy has been defined clinically as congestive heart failure occurring in patients with coronary artery disease without coexisting hypertension primary valvular disease ventricular aneurysm formation or known causes of cardiomyopathy Morphologic definition of this entity is scarce We reviewed over 200 patients with coronary artery disease who came to autopsy at this hospital and identified 14 who met the above criteria At autopsy all the hearts showed diffuse biventricular dilatation without aneurysm formation All had evidence of recurrent infarction in more than one vascular distribution and postmortem angiography revealed extensive coronary artery disease The amount of infarcted myocardium determined by planimetry ranged from 8% to 46% Although the hearts were enlarged with an average weight of 600 grams the non infarcted ventricular myocardium was thinner than seen in normals in patients with ischemic heart disease without cardiomyopathy in patients with idiopathic congestive cardiomyopathy and in those with dilatation due to valvular regurgitation The results suggest that ischemic cardiomyopathy does not merely reflect a critical amount of myocardium lost but rather severe diffuse coronary artery disease accompanied by multiple sites of infarction which together lead to progressive dilatation disproportionate wall thinning and inadequate compensatory wall thickening Thus these patients appear to have a true cardiomyopathy in that the entire left ventricle (infarcted and non infarcted tissue) appears to be adversely affected by the ischemic process insofar as there is a diffuse globular remodeling of the heart

REFERENCES

1 Raftery E B., Banks, D C and Oram, S. Occlusive disease of the coronary arteries presenting as primary congestive cardiomyopathy Lancet 29 114 197[illegible]
2. Burch, G E., Giles, T D., and Colcolough, H. L. Ischemic cardiomyopathy AM HEART J 79 291 1970
3 Yatteau R. F., Peter R. H. Behar V S., Bartel A G., Rosati, R. A., and Kong Y Ischemic cardiomyopathy The myopathy of coronary artery disease, Am J Cardiol 34 520 1974
4 Faulkner S L., Stowey W S., Alford, W C Thomas C S., Burrus G R Frist R A and Page H. L. Ischemic cardiomyopathy Medical versus surgical treatment J Thorac Cardiovasc. Surg 74 77 1977
5 Dash, H., Johnson, R A., Dinsmore R. E., Francis C K and Harthorne, J W. Cardiomyopathic syndrome due to coronary artery disease Br Heart J 39 733, 1977
6. Burch, G E., Tsui, C Y., and Harb J M Ischemic cardiomyopathy AM. HEART J 83 340 1972.
7 Bulkley B H., Hutchins, G M., Bailey I., Strauss H W and Pitt B Thallium 201 imaging and gated cardiac blood pool scans in patients with ischemic and idiopathic congestive cardiomyopathy Circulation 55 753, 1977
8 Ellis L. B., Allison R B Rodriquez, F L., and Robbins S L. Relation of the degree of coronary artery disease and of myocardial infarction to cardiac hypertrophy and chronic congestive heart failure N Engl J Med 266 525 1962
9 Rackley C E., Dear H D., Baxley W A., Jones W B and Dodge H T Left ventricular chamber volume mass, and function in severe coronary artery disease Circulation 41 605 1970
10 Field B J., Baxley W A., Russell, R. O Hood, W P Holt J H., Dowling J T., and Rackley C E. Left ventricular function and hypertrophy in cardiomyopathy with depressed ejection fraction, Circulation 47 1022 1973
11. Hatle L., Orjavik, O., and Storstein, O Chronic myocardial disease I Clinical picture related to long term prognosis II Hemodynamic findings related to long term prognosis, Acta Med Scand 199 399 1976
12. Page D L., Canfield J B., Kastor J A DeSanctis R W., and Sanders C A Myocardial changes associated with cardiogenic shock, N Engl J Med. 285 133, 1971
13 Castleman B., and McNeely B U. Case records of The Massachusetts General Hospital Case 51 1970, N Engl J Med. 283 1392, 1970

Table III Ventricular wall thickness of non infarcted myocardium

	Group I — Ischemic cardio myopathy	Group II— Recurrent infarctions	Group III— Primary valvular insufficiency (aortic or mitral insufficiency)	Group IV — Idiopathic dilated cardiomyopathy
nterior wall thickness (mean)	1 20 cm (±0 10)	1 7 cm (±0 10)	1 9 cm (±0 10)	1 7 cm (±0 10)
osterior wall thickness (mean)	1 10 cm (±0 20)	1 7 cm (+0 11)	1 9 cm (±0 10)	1 6 cm (±0 10)
ateral wall thickness (mean)	1 10 cm (±0 10)	1 7 cm (±0 11)	2 0 cm (±0 10)	1 7 cm (±0 10)
eptal wall thickness (mean)	1 10 cm (±0 10)	1 6 cm (+0 07)	1 9 cm (±0 10)	1 6 cm (±0 10)

Group I measurements w re significantly less than those in the oth r three groups ($p < 0 01$)

nd were in the distribution of more than one najor coronary artery It appears that when the ntire loss of myocardium is in one vascular listribution the area of regional injury shows naximal dysfunction and the non infarcted nyocardium undergoes compensatory wall thick ning If cardiac dilatation occurs it is apt to be egional or aneurysmal If the injury occurs in nultiple vessel distribution in the setting of extensive coronary disease diffuse rather than egional dilatation is apt to occur That such lysfunction and diffuse dilatation can occur with is little as 20% loss of left ventricle might suggest hat diffuse ischemia combined with multisite njury might contribute to the progressive cardiac lilatation of ischemic myocardiopathy

What is perhaps one of the most striking feature of the heart in ischemic myocardiopathy is that it takes on the over all globular configura tion of a dilated congestive cardiomyopathic heart (Fig 2) a configuration to be readily distin guished from the heart with discrete left ventric ular aneurysm which might have as severe dys function and as great a total extent of infarction (Fig 3) Although the clinical presentation of these two entities left ventricular aneurysm and ischemic cardiomyopathy may be indistinguish able their morphologic characteristics and likely their potential for surgical remedy are markedly different With improved noninvasive techniques which provide information on over all shape such as the two dimensional echocardiogram and the thallium 201 myocardial perfusion scan ' the two entities should be identifiable

All 14 hearts were markedly enlarged with an average weight of 625 grams but left ventricular wall thicknesses were disproportionately thin for heart weight even in areas not directly thinned by necrosis or fibrosis The average maximal wall thickness in these hearts was significantly thinner than the values obtained from a group of autop sied patients with recurrent infarctions but with out a myocardiopathy picture ($p < 0 01$) and the walls were thinner than the values obtained for autopsied patients with idiopathic dilated cardio myopathy ($p < 0 001$) and with primary valvular disease ($p < 0 01$)

Congestive heart failure and myocardial infarc tion are a recognized stimulus for myocardial hypertrophy in patients with coronary artery disease The ability of surviving myocardium to hypertrophy in response to injury of part of the left ventricle is a compensatory mechanism how ever only to a point in that it leads to additional tissue requiring additional coronary flow Rack ley and co workers have shown that the degree of left ventricular hypertrophy relative to left ven tricular end diastolic volume was a prognostic indication of post catheterization survival rates with greater hypertrophy for a given end diastolic cavity enlargement carrying a better outlook It has also been shown in patients with primary myocardial disease that the ability of the heart to compensate for its dilatation by developing wall hypertrophy correlated positively with sur vival ' The patients with ischemic cardiomyopa thy studied at autopsy appear to fall into that poorer prognostic group in which the heart is dilated but it not able to appropriately thicken adjacent non infarcted wall Although in primary cardiomyopathy one might suspect that the ina bility of some patients to develop compe

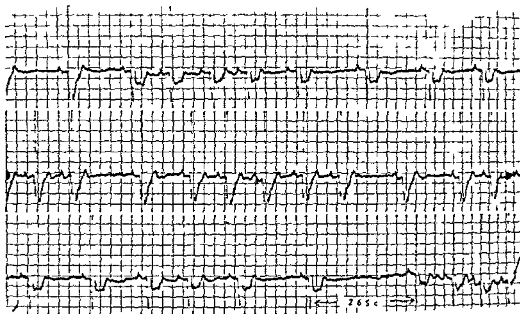


Fig 1 The electrocardiogram indicates frequent sinus pauses (the longest being 2 6 seconds)

at the nose or mouth with a CO_2 analyzer Thoracic breathing movements were determined by measuring transpulmonary pressure changes with an intraesophageal balloon Upper airway obstruction was defined as a cessation of airflow at the nose and mouth in the presence of continued thoracic breathing movements All investigational procedures were carried out with the subject s informed consent under protocols approved by the local Human Experimentation Committee The pre tracheostomy study revealed 312 upper airway obstructions with a mean duration of 16 seconds with a range of 10 to 27 seconds Obstructions were accompanied by prolonged asystole (up to seven seconds) with second degree AV block and marked sinus arrhythmias (Fig 2) O saturations during sleep ranged from 82% to 93% The post tracheostomy study revealed no upper airway obstructive episodes and no clinically significant central apneas or other respiratory abnormalities. There were no significant cardiac arrhythmias The ear oximeter revealed no oxygen desaturations during the study

Electrophysiologic studies From a right femoral vein puncture a tripolar catheter was positioned on the septal leaflet of the tricuspid valve and resting A H and H V intervals were recorded The A H interval representing AV nodal conduction was 140 msec and the H V interval representing His-Purkinje conduction was normal at 50 msec This catheter was switched for a hexapolar catheter which was positioned in the high right atrium in order to study the response of the sinus node to overdrive pacing The patient had a maximum sinus recovery time of 910 msec and a correct sinus recovery time of 260 msec, which indicated normal sinus node function She had normal atrioventricular conduction during rapid atrial pacing

Discussion

There is little information on arrhythmias in the sleep apnea syndrome Kryger and associates[4] reported a case of an obese man who had somnolence and upper airway obstruction His apnea episodes were usually associated with bradyarrhythmias He had atrial fibrillation and flutter with a high degree AV block and asystole lasting up to ten seconds The arrhythmias were abolished by atropine but electrophysiologic studies were not performed Tilkian and colleagues[5] studied cardiac arrhythmias during wakefulness and sleep in 15 patients with sleep induced obstructive apnea Sleep was characterized by marked sinus arrhythmia in 14 by extreme sinus bradycardia in six by asystole or 2.5 to 6 3 seconds in five by complex PVC s in ten and by ventricular tachycardia in two Atropine was partially effective and tracheostomy highly effective in preventing the majority of these arrhythmias during sleep Tilkian and co workers[5] also postulated that these arrhythmias are not due to fixed or anatomic disease of the sinoatrial or AV nodes but that they reflect functional and reversible abnormalities precipitated by sleep-related abnormal CNS functioning They suggested that airway obstruction caused hypoxia which stimulated vigorous inspiratory effort against the closed airway This inspiratory effort activated vagal parasympathetic impulses causing sinus bradycardia Hypoxia and acidosis may also increase sympathetic tone, causing sinus tachycardia PVC s and ventricular tachycardia

Table 1 illustrates the data in our patients

Case reports

Arrhythmias in sleep apnea

Tsutomu Imaizumi M D
Oklahoma City Okla

The original description of the Pickwickian syndrome included obesity periodic breathing with hypoventilation somnolence and cor pulmonale[1] It is now well established that the essential features of this syndrome—i e somnolence hypoventilation and cor pulmonale—can occur in the absence of obesity and with normal carbon dioxide responsiveness[2] This syndrome has been recently called the sleep apnea hypersomnolence syndrome (SAHS) because of the occurrence of obstructive apnea in these patients during sleep Disturbances in cardiac rhythm can occur during sleep[3,4] and multiple arrhythmias have been described in association with the SAHS In this report I describe detailed sleep studies electrophysiologic studies and the clinical data of a patient with the SAHS and briefly present arrhythmias of other patients with this syndrome

Case report

History A 23 year-old black female was admitted to the University Hospital on December 9 1976 because of "sleep trouble" She complained of falling easily to sleep even when she was teaching at a kindergarden Her mother noticed that she fell asleep very easily when she was working She had frequent morning headache Her mother also confirmed that th patient snored noisily and had frequent periods of apnea A hospital record indicated that she had been obese for many years prior to that time She had adenocarcinoma of the endometrium with polycystic ovarian disease and underwent a total vaginal hysterectomy with bilateral salpingo ophorectomies in 1974 Physical examination on admission revealed a very obese black female who appeared older than her stated age and weighed 174 kg The blood pressure was 130/90 mm Hg pulse was 9? per/minute and respiratory rate was ?2 per/minute The skin was dry The head eyes ears nose and throat were unremarkable There was thyromegaly but no palpable nodes The carotid pulses were 2+ bilaterally The chest was symmetrical with equal bilateral expansion The breasts were huge and pendulous without palpable masses The lungs were clear to auscultation and percussion The heart was regular in rhythm without murmurs or gallops The abdomen was massive with fat pads The extremities were obese without edema Neurological examination was within normal limits She had a normal CBC with differentiation SMA18 T3 and T4 Arterial blood gases revealed pH 7 47 PCO_2 37 mm Hg PO_2 72 mm Hg and HCO_3 2? mEq/L Electrocardiograms were all within normal limits with sinus rhythm A chest x ray was free of active infiltrates and the heart size was normal Pulmonary function studies revealed a reduced total lung capacity functional residual capacity residual volume and expiratory residual volume all compatible with mild restrictive disease The diffusing capacity and airway resistance were within normal limits

A sleep study was performed She experienced over 300 episodes of upper airway obstruction with some lasting over 30 seconds These were accompanied by severe cardiac arrhythmias The details will be described subsequently Tracheostomy was performed because of disabling somnolence and severe cardiac arrhythmias She was discharged without medications She had lost some weight and did well with marked reduction in daytime somnolence and headache Hypersomnolence was quickly resolved and the post tracheostomy sleep study revealed no cardiac arrhythmias

Approximately one week prior to her second admission on April 15 1977 she developed constant throbbing headaches with blurred vision She came to the emergency room where her pulse was noted to be slow An electrocardiogram showed frequent sinus pauses (Fig 1) She was admitted to the Intensive Care Unit Physical examination showed that she was somewhat confused Blood pressure was 112/70 mm Hg and her pulse was irregular She weighed 163 kg at this time Other physical findings were unchanged from those of the previous admission Arterial blood gases revealed pH 7 49 PCO_2 8 mm Hg PO_2 ?1 mm Hg and HCO_3 20.5 mEq/L The ECG monitor showed frequent episodes of sinus bradycardia sinus pauses and second-degree heart block not associated with respiration or hypoxia One milligram of atropine was given without effect

Sleep studies In order to determine the presence and extent of upper airway obstruction during sleep the patient was studied in the Sleep Physiology Laboratory Recordings included continuous monitoring of the ECG EEG EOG and EMG for determination of sleep stages The presence of airflow was assessed by recording fluctuations of expired CO_2

From the University of Oklahoma Health Sciences Center Cardiovascular Section Oklahoma City Okla

Received for publication Feb 1979
Accepted for publication June 22 1979

Reprint requests Tsutomu Imaizumi M D 3 1 1 Maidashi, Higashi ku, Cardiovascular Institute Fukuoka Japan 81

Table I

Name	*Age*	*Sex*	*Med*	*ECG*	*Arrhythmia during sleep studies*	*Trach*	*Arrhythmia after trach*	*Weight*
J R	47	M	Amino Dig	Mild RVH	7 sec SP SB 30 Slow VT	(+)	(–)	137 kg
B B	30	M	None	NL	3 6 sec SP	(–)		133 kg
H.C	24	F	None	1st A V block	7 0 sec. ASY 2 A V block	(+)	(+)	163 kg
O C	58	M	None	IRBBB	1 6 sec SP	(–)		120.? kg
C U	30	M	None	Mild RVH	6 5 sec SP	(+)	(–)	99 kg
C T	64	M	None	NL	Freq PVC s VT	(–)		190 kg
F W	48	M	None	NL	Junct Rhy	(–)		125 kg

Abbreviations Amino = aminophyllin Dig = digitalis NL = normal RVH = right ventricular hypertrophy IRBBB = incomplete right bun[dle] branch block SP = sinus pause SB = sinus bradycardia VT = ventricular tachycardia Junct Rhy = junctional rhythm Trach = tracheosto[my] Freq = frequent
See text for details

not have clinical evidence of organic heart disease, sinoatrial or AV nodal disease is not likely I can hypothesize that increased parasympathetic impulses because of vigorous inspiratory effort against the closed airway caused sinus bradycardia prolonged sinus pause and AV block After abrupt cession of the airway obstruction the parasympathetic tone decreased and there would have been overshoots of sympathetic impulses which could have caused frequent premature ventricular contractions and ventricular tachycardia

Conclusion

Severe cardiac arrhythmias can be seen in patients with sleep apnea These are not likely to be caused by the organic sinoatrial or AV node disease but are due to functional and reversible abnormalities precipitated by the sleep dependent CNS dysfunction Tracheostomy may be effective in controlling the arrhythmias in some patients with obstructive sleep apnea

Summary

A 23 year old black female was referred to the University Hospital of Oklahoma because of sleep trouble She complained of falling asleep easily during the daytime A sleep study was performed which showed prolonged apnea up to 35 seconds and prolonged asystole up to seven seconds with second degree heart block A tracheostomy was performed She had lost so[me] weight and did well until six months later wh[en] she developed severe throbbing headache w[ith] visual blurring She came to the emergency ro[om] and an ECG showed sinus bradycardia w[ith] prolonged sinus pauses up to 2 6 seconds, a[nd] first and second degree AV block She had [no] hypoxia and atropine was ineffective Electrophy[-] siologic studies were performed Details of t[he] case are described and mechanisms of t[he] arrhythmias are discussed

I am grateful to Drs William Orr and Eliot Schec[hter for] reviewing the manuscript

REFERENCES

1 Burwell, C S Robin E D Whaley R. D and Bick[el]mann A G Extreme obesity associated with al[veolar] hypoventilation a Pickwickian syndrome Am J M[ed] 21 811 1956
2 Guilleminault C Tilkian A and Dement W C. T[he] sleep apnea syndrome Ann Rev Med 27 465 1976
3 Tzivoni, D and Stern S Electrocardiographic patt[erns] during sleep in healthy subjects and in patients w[ith] ischemic heart disease J Electrocardiol 6 225 1973
4 Snyder F Hobson J A Morrison D F and Go[ld]frank F Changes in respiration heart rate and syst[olic] blood pressure in human sleep J Appl Physiol 19 (1964
5 Tilkian A G Guilleminault C Schroeder J S Le[h]man K L Simmons F B and Dement, W C Sleep-induced apnea syndrome prevalence of card[iac] arrhythmias and their reversal after tracheostomy A[m] J Med 63 348 1977
6 Kryger M Quesney L. F Holder D Gloor P a[nd] MacLeod P The sleep deprivation syndrome of t[he] obese patient Am J Med 56 531 1974

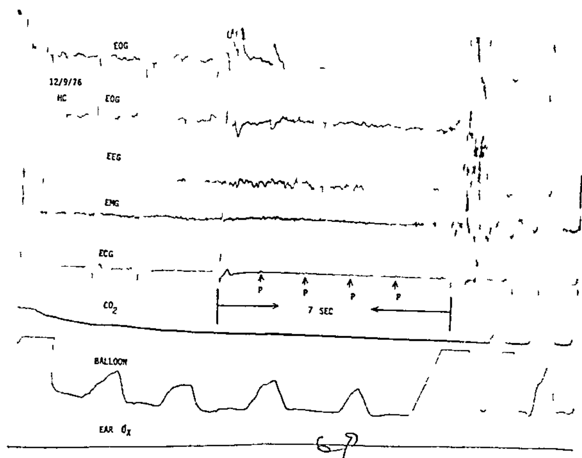


Fig 2 Polygraphic sleep study The flat line of CO indicated prolonged apnea in the presence of breathing efforts shown by fluctuations in the line of the balloon There were 7 seconds of asystole associated with apnea As soon as the patient started breathing normal sinus rhythm was restored *EOG = electrooculogram EEG* = electroencephalogram *EMG* = electromyogram *CO* = CO analyzer *BALLOON* = intraesophageal balloon *P* = P wave

They are all obese (except patient C U) and young (except patient C T) and none had a history suggesting ischemic heart disease and none were on cardiac medication except patient T R Waking ECG s were not impressive During sleep they all had significant cardiac arrhythmias Sinus arrhythmia (not listed here) occurred in all patients in association with episodes of upper airway obstruction Patients C V and T R had no arrhythmias after a tracheostomy

Only patient H C (the subject of this case report) had electrophysiologic studies She had prolonged asystole (seven seconds) with second degree AV block before tracheostomy Arrhythmias persisted after tracheostomy however they were much milder We gave atropine intravenously which was not effective and arrhythmias were not associated with hypoxemia This suggests another mechanism of arrhythmia in the patient

Since electrophysiologic studies were normal during wakefulness sinoatrial or AV nodal disease is not likely Then what are the mechanisms of arrhythmia in the patient? As shown in Fig 2 she had airway obstruction with inspiratory effort evidenced by the flat CO line and the cyclic shift of the line of balloon During this airway obstruction the parasympathetic nerve must have been activated which could have caused second degree heart block with prolonged asystole It is interesting to note that she was well for six months after a tracheostomy and when she developed arrhythmias she had severe headache and she was somewhat confused Thus we can hypothesize that an acute central nervous event may have caused these arrhythmias although she had no other evidence of CNS dysfunction

How about the mechanism of the other patients? Since most of them are young and did

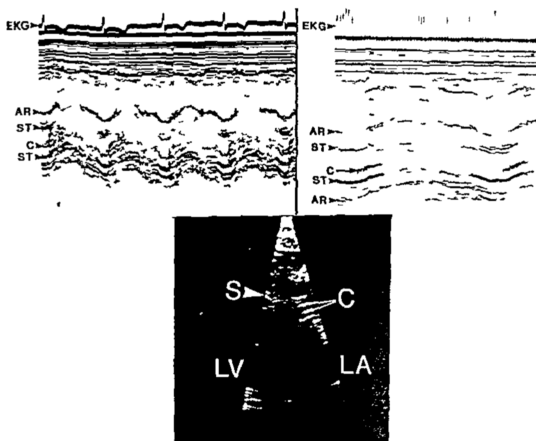


Fig 1 M mode and two dimensional echocardiogram of the stenotic porcine aortic valve are shown. *Left upper panel* increased cu p echoes with restricted cusp motion during systole are depicted *Right upper panel* after reducing the coarse gain the high frequency low amplitude fluttering of the thickened cu ps (C) are visualized. *Lower panel* a systolic frame of the two dimensional echocardiogram is shown Note the marked reduction (< 10 mm.) of the cusp opening AR = aortic root C = cusps EKG = electrocardiogram LA = left atrium LV = left ventricle S = ventricular septum ST = porcine valve stents

phy but was clearly reduced on the two dimensional study This is comparable to the previous reports in which the two dimensional echocardiography because of its greater spatial orientation was found to be more useful than the M mode study in assessing the valve opening and stenosis of the native aortic valve The systolic opening of the porcine cusp however as with the native aortic valve may be influenced by left ventricular stroke volume The left ventricular function and stroke volume were normal in our patient and would not account for the reduced cusp opening of the porcine valve

The significance of the systolic fluttering noted on the M mode study of our patient cannot be determined Similar flutter has been reported in a normal native aortic valve but has not been observed in a normally functioning porcine aortic valve[5] It is possible that the systolic flutter may be a normal finding which has not yet been reported in the relatively small number of echocardiographic reports dealing with the functio[n]ly normal porcine bioprosthesis in the ao[rtic] position Another possible explanation of systolic flutter may be as a result of turbulen[t] blood flow across the stenotic and thicke[ned] porcine cusps Further studies are needed in [this] area before firm conclusions can be drawn

The etiology of porcine valve stenosis is [not] exactly clear Most likely it is a result o[f a] degenerative process similar to that previou[sly] reported by light and electron microscopic st[udies] of these valves[6]

In conclusion both modes of echocardiograp[hy] are of value in evaluating stenosis of the porc[ine] aortic valve a condition which may be amen[able] to valve replacement surgery

Summary

M mode and two-dimensional echocard[io]graphic features are reported in a patient [who] developed severe stenosis of a porcine xenogr[aft]

Echocardiographic features of a stenotic porcine aortic valve

Mohsin Alam M D
Sidney Goldstein M D
Detroit Mich.

The echocardiographic features of porcine valve degeneration have recently been reported These reports have confined their descriptions to aortic insufficiency, mitral stenosis and insufficiency occurring in the degenerating porcine xenograph Although stenosis of the porcine valve in the aortic position has been noted to occur the echocardiographic features were not described due to the inability to visualize the valve adequately Subsequent to our initial reports we have observed an additional patient with stenotic degeneration of the porcine xenograph in the aortic position that occurred 60 months after implantation

Case history

D D a [illegible]9-year-old male underwent an aortic valve replacement with a porcine xenograph (Hancock) valve Six years later he was seen again complaining of pressure like chest pain and dyspnea on minimal exertion He also complained of frequent light headed spells, without syncope There was no history of paroxysmal nocturnal dyspnea, fever or chills

Physical examination revealed a blood pressure of 120/80 mm Hg pulse 80/minute and regular The carotid pulse upstroke was prolonged and a systolic thrill was palpable in the second right intercostal space The aortic component of the second heart sound was diminished A grade IV/VI systolic ejection murmur radiating to the carotid vessels and grade II/VI diastolic blowing murmur were present at the second right intercostal space and the lower left sternal border The diastolic murmur had not been present on a physical examination performed a year previously and the intensity of the systolic murmur had increased.

Pertinent laboratory studies including hemoglobin platelet total and differential white blood count and blood cultures were all within normal limits The electrocardiogram revealed left ventricular hypertrophy with strain pattern Chest x ray revealed left ventricular enlargement and on fluoroscopy porcine valve calcification was noted Cardiac catheterization revealed a peak porcine aortic valve gradient of 88 mm Hg with calculated valve area of 0 [illegible]3 square centimeters. Angiography revealed moderate porcine aortic valve insufficiency with normal coronary arteries.

An M mode and a two-dimensional echocardiogram using conventional techniques and instrumentation (Smith Kline Ekoline 20-A and Ekosector I) were performed within one week of cardiac catheterization and porcine valve replacement surgery Both modes of echocardiography revealed an increase in porcine cusp echoes (Fig 1) The M mode study in addition revealed high frequency low amplitude systolic fluttering of the cusps The opening of the valve could not be accurately measured on the M mode study due to increased echoes from the thickened cusps. The systolic opening of the porcine cusps however was clearly visualized and was markedly reduced on the two-dimensional study (Fig. 1)

The gross examination of the porcine valve at the time of surgery revealed thickened and stenotic cusps with multiple calcific nodules and scarred retraction of the cusp margins (Fig 2)

Discussion

M mode echocardiography has been reported to be useful in evaluating a stenotic mitral porcine valve[1] Although severe stenosis of a porcine valve has also been reported in the aortic position[1] the echocardiographic features of this entity have not been reported The increased cusp echoes in our patient were associated with thickening and calcification of the valve cusps which was demonstrated at the time of surgery Echocardiographic features of the stenotic porcine valve in the mitral position have shown a similar increase in cusp echoes with identical gross anatomic findings.[3] As a result of increased cusp echoes, the porcine valve opening could not be clearly demonstrated by M mode echocardiogra

From the Division of Cardiovascular Medicine and the Department of Medicine, Henry Ford Hospital, Detroit Mich

Received for publication May 2, 1979
Accepted for publication Aug. 1 1979

Reprint requests Mohsin Alam, M D Henry Ford Hospital, ?799 W Grand Blvd Detroit, Mich 48?0?

0002 8703/80/100?17 + 03$00 30/0 1980 The C V Mosby Co

Intraventricular thrombosis in polycythemia vera A cause of intractable cardiac failure

Majid Ali M D *
A. Olusegun Fayemi M D **
Daniel Malcolm***
Evalynne V Braun M D ****
Teaneck N J

Case report

A 72 year-old man was hospitalized for massive edema of the legs, increase in abdominal girth of recent onset weakness and anorexia He had previously been healthy and he specifically denied antecedent hypertension or heart disease A diagnosis of congestive heart failure was made on the basis of findings of cardiomegaly pitting dependent edema ascites hepatomegaly and bilateral basal pulmonary rales

Pertient laboratory data were as follows hemoglobin 18 4 Gm /dl. hematocrit 63% RBC 6 73 million/cu mm WBC 13 100/cu mm with 48% mature neutrophils 6% bands 18% lymphocytes 2% eosinophils and 1% basophils platelets 30 000/cu mm Leukocyte alkaline phosphatase score was 162 (control 76) Total blood volume was 19,500 ml (predicted value 5 700 ml.) the red cell mass was 9 000 ml (predicted value 2 500 ml) The results of serum chemical analysis were as follows LDH 790 MU /ml (laboratory normal 90 to 200 MU /ml) SGOT 90 MU /ml (laboratory normal 10 to 50 MU /ml) total bilirubin 3.8 mg /dl total protein 5 8 Gm / dl albumin 2 94 Gm /dl uric acid 9 5 mg /dl. BUN 19 mg./dl calcium 8 1 mg./dl and alkaline phosphatase 90 MU /ml (laboratory normal 30 to 85 MU /ml.) The serum electrolyte values were within normal limits except for a slightly elevated value for serum sodium of 148 mEq /L. Chest roentgenogram demonstrated an enlarged heart [illegible] pleural effusion Gastrointestinal series and intraveno[us] ogram studies were normal except for displacement [illegible] ach and left kidney by an enlarged spleen Liver sc[an] Au [illegible] showed hepatomegaly without focal intra[hepatic] lesions The ECG showed ST T wave abnormalities [illegible] marrow aspiration was dry but a biopsy showed prom[inent] erythroid hyperplasia megakaryocytosis, eosinophil[ia] fibrosis

With the clinical diagnosis of congestive heart [failure] secondary to arteriosclerotic coronary artery diseas[e] patient was treated with digitalis diuretics and phlebot[omies] Lowering of hematocrit to below 50% was achieved by pe[riodic] phlebotomies However the congestive failure proved intractable and he died 6 months later of refractory cong[estive] failure with left pleural effusion massive ascites, and an[asar]ca

Pathology

At autopsy the heart was hypertrophied and weighed [illegible] grams the maximum thickness of the right and the [left] ventricular wall being 0 3 and 1.8 cm respectively A mas[sive] intramural thrombus covering the endocardial surface of [the] left ventricle in its entirety was observed The thro[mbus] extended from the apex of the heart and reduced the capa[city] of the left ventricle by about 70% (Fig. 1) Microscopica[lly the] thrombus displayed various stages of organization the su[rface] exposed to the blood flow was well endothelialized 45 [illegible] major branches of both the right and left coronary arte[ries] showed minimal arteriosclerotic changes No significant n[ar]rowing of the arterial lumina was demonstrable The myoca[r]dium beneath the intramural thrombus was studied by mu[lti]ple sections No evidence of any recent or remote infarct wa[s] observed

In the gross examination of the various viscera, seve[re] passive venous congestion was observed especially in the lungs and the liver The liver weighed 2,400 grams and cr[oss] section showed a nutmeg appearance The large pu[lmonary] arteries showed prominent arteriosclerotic plaques The spleen was massively enlarged weighed 1,200 grams and se[v]eral sections, displayed many areas of infarction His[tologi]cally pronounced extramedullary hematopoiesis and [illegible]

From the Departments of Pathology and Medicine of the Holy Name Hospital, Teaneck, N J

Received for publication June 4 1979

Accepted for publication July 19 1979

Reprint requests D Majid Ali Director of Laboratories Holy Name Hospital Teaneck N J 07666

Director of Laboratories H[oly] N[a]me Hospital Teaneck N J Asst. Professor of P[atho]log[y] (Adj) C[o]llege of Physicians and Surgeons Columbia University New York N Y

Attending Path[ologist] H[oly] N[a]me Hospital Teaneck, N J Asst Clinical Profess[or] [of] [Patho]l[o]gy The Mount Sinai School of Medicine New York N Y

Attending Ph[ysician] [Dep]a[rtme]nt of Medicine Holy Name Hospital, Teaneck, N J

Attending Path[olo]g[ist] H[oly] [Na]m[e] Hospital Teaneck N.J Asst Professor of Pathology [Fairlei]gh Dickinson School of Dentistry Teaneck, N J

0002 8703 80 100 70 + 0 500 @ 0 r 1 50 The C V Mosby C[o]



Fig 2 This figure shows the gross appearance of the stenotic porcine valve The cusps are thickened with multiple calcific nodules and retracted cusp margins

valve implanted in the aortic position The presence of increased cusp echoes along with reduced cusp opening was the most consistent echocardiographic finding in this patient The clinical and the echocardiographic findings were subsequently confirmed by cardiac catheterization and surgery

REFERENCES

1 Alam M Madrazo A C Magilligan D J., and Goldstein S M mode and two-dimensional echocardiographic features of porcine valve dysfunction Am J Cardiol 43 502 1979
2 Weyman A E Dillon J C Feigenbaum H and Chang S Cross sectional echocardiography in assessing the severity of valvular aortic stenosis Circulation 52 828 1975
3 Horowitz M S Tecklenberg P L, Goodman D J Harrison D C and Popp R L Echocardiographic evaluation of the stent mounted aortic bio-prosthetic valve in the mitral position In vitro and in vivo studies Circulation 54 91 1976
4 Pinto E. R., Damani P M Sternberg C N., and Liedtke A J Fine flutterings of the aortic valve as demonstrated by aortic valve echocardiograms, Am Heart J 95 807 1978
5 Chandraratna P A N and San Pedro S B Echocardiographic features of the normal and malfunctioning porcine xenograft valve Am Heart J 95 548 1978
6 Fishbein M C., Gissen S A Collins, J J Barsamian E M., and Cohn L. H Pathologic findings after cardiac valve replacement with glutaraldehyde fixed porcine valves, Am J Cardiol. 40 331 1977
7 Ferrans V J Spray T L., Billingham M E and Roberts W C Structural changes in glutaraldehyde treated porcine hetrografts used as substitute cardiac valves. Transmission and scanning electron microscopic observations in twelve patients Am J Cardiol 41 1159 1978

Summary

The occurrence of thrombotic events is central to the course of polycythemia vera[1] Myocardial cerebral peripheral and pulmonary infarctions are frequent and are consequences of thromboses in small and medium caliber arteries Thrombosis in large caliber arteries is a rare event Thrombosis within the chambers of the heart has not been hitherto reported

This report documents the occurrence of massive left ventricular thrombosis in a patient with polycythemia vera The thrombus reduced the left ventricular capacity by about 75% and caused intractable congestive heart failure

The help of Gertrude Martin is gratefully acknowledged in preparation of the manuscript

REFERENCES

1. Burns M D., and Arrowsmith, W R Vascular complications of polycythemia vera Surg Clin North Am 33 1023 1953
2. Brown G E and Griffin H Z. Peripheral arterial disease in polycythemia vera Arch. Intern Med. 46 705 1930
3. Chievitz, E., and Thiede, I Complications and causes of death in polycythemia vera Acta Med. Scand 172 513 1962.
4. Videlack, A. Polycythemia vera. Course and progn Acta Med Scand. 138 179 1950
5. Wasserman L. R. and Bassen, F Polycythemia, J Sinai Hosp N Y 26 1 1959
6. Murray J D Gold, P., and Johnson, B L, Jr circulatory effects of hematocrit variations in norm lemic and hypervolemic dogs, J Clin. Invest. 42 1963
7. Altschule M D., Volk, M C and Henstell, H. Ca and respiratory function at rest in patients with un plicated polycythemia vera Am J Med. Sci. 200 1940
8. Adams C W., Collins, H A., Dummit E S and All H. Intracardiac myxomas and thrombi. Clinical festations pathology and treatment, Am. J Ca 7 176 1961
9. De Paiva F C., Macieira Coelho E Amram S S Duarte C da S Intracavitary left ventricular my Am J Cardiol. 20 260 1967
10. Childress R H., King R D Aldrich, D D Buehl, King H. and Genovese P A Successful resection benign right ventricular mesenchymoma Am. J Ca 20.255 1967
11. Parry E H. O and Abrahams D G The na history of endomyocardial fibrosis Q J Med. 36 1965
12. De Maria A. N Bommer W., Newmann A., Greh Weinart L. De Nardo S., Amsterdam E. A., and M D T Left ventricular thrombi identified by c sectional echocardiography Ann. Intern Med. 9 1979



Fig 1 Massive intraventricular thrombus The thrombus urface is smooth and well-endothelialized *(AA)* the underlying myocardium shows no evidence of recent or old infarction *(BB)*

sinusoidal proliferation was observed in the spleen the plenic infarcts showed various stages of organization Extramedullary hematopoiesis was also observed in the liver the lungs and the retroperitoneal and mediastinal lymph nodes In the lungs muscular hyperplasia of peripheral, subpleural arteri oles was observed The marrow displayed pronounced hyper plasia involving all the marrow elements megakaryocytes and eosinophils were especially abundant

Discussion

Cardiac function and cardiac output are usual ly normal in polycythemia vera [6] The clinical course of the patient reported in this paper was highly unusual while the diagnosis of polycy themia vera was readily made by the hematologic udies and blood volume determinations the ue nature of its relationship with congestive eart failure remained masked The probability of e cardiac failure being secondary to arterioscle otic coronary artery disease or the existing ematologic disorder was clinically suspected hough the electrocardiographic evidence for this as lacking At autopsy the clinical picture of efractory heart failure was related to the pres nce of the left ventricular thrombus per se eference to the literature on intracardiac umors and thrombi shows that tumors in the ight heart are associated with weakness edema epatomegaly and ascites Space occupying esions in the left heart are associated with dysp ea orthopnea and with emboli to the central ervous system renal mesenteric and peripheral rteries In view of the closer correspondence of his patient s clinical manifestations to those of patients with compromised right ventricular function we offer the hypothesis that this patient s thrombus either interfered with mitral valve function or so gradually but progressively interfered with left ventricular filling that the process became a physiological equivalent of mitral stenosis with the subsequent development of pulmonary hypertension and right ventricular failure From a functional standpoint the patho genetic mechanism for the intractable heart fail ure seen in this patient is closely analogous to the hemodynamic impairment observed in patients with endomyocardial fibrosis [7] In this entity found primarily among Africans the fibrotic pro cess with or without thrombus formation may so seriously reduce the ventricular capacity as to prove fatal

Rheologic factors are known to play an impor tant role in the local propagation of clotting It is likely that this clot formed slowly by accretion on a small starting nidus The large size of the clot the many stages of organization seen in the thrombus the completely endothelialized sur face the absence of an acute arterial occlusive event and the prolonged (6 month) course of this patient are all consistent with this hypothesis The nature of the event initiating the intraven tricular clotting was obscured by the reparative processes within the clot

Had echocardiographic studies been performed the clot might have been detected [8] Its removal might have restored the left ventricular capacity and relieved intractable congestive failure

Summary

The occurrence of thrombotic events is central to the course of polycythemia vera[1] Myocardial cerebral peripheral and pulmonary infarctions are frequent and are consequences of thromboses in small and medium caliber arteries Thrombosis in large caliber arteries is a rare event Thrombosis within the chambers of the heart has not been hitherto reported

This report documents the occurrence of massive left ventricular thrombosis in a patient with polycythemia vera The thrombus reduced the left ventricular capacity by about 75% and caused intractable congestive heart failure

The help of Gertrude Martin is gratefully acknowledged in preparation of the manuscript

REFERENCES

1. Burns M D and Arrowsmith W R Vascular complications of polycythemia vera Surg Clin North Am **33** 1023 1953
2. Brown G E and Griffin H Z Peripheral arterial disease in polycythemia vera Arch Intern Med **46** 705 1930
3. Chievitz E and Thiede, I Complications and causes of death in polycythemia vera Acta Med Scand **172** 513 1962.
4. Videlack, A Polycythemia vera Course and prognosis Acta Med Scand **138** 179 1950
5. Wasserman L. R and Bassen, F Polycythemia, J Mt Sinai Hosp N Y **26** 1 1959
6. Murray J D Gold P and Johnson, B L., Jr The circulatory effects of hematocrit variations in normovolemic and hypervolemic dogs, J Clin. Invest. 42 1150 1963
7. Altschule M D Volk M C and Henstell, H. Cardiac and respiratory function at rest in patients with uncomplicated polycythemia vera Am J Med. Sci. 200 (?) 1940
8. Adams C W Collins H A Dummit, E S and Allen, J H Intracardiac myxomas and thrombi. Clinical manifestations, pathology and treatment, Am. J Cardiol 7 176 1961
9. De Paiva E C., Macieira Coelho E Amram, S S, and Duarte C da S Intracavitary left ventricular myxoma Am J Cardiol **20** 260 1967
10. Childress R H., King R D Aldrich D D Buehl, I A, King H and Genovese P A Successful resection of a benign right ventricular mesenchymoma Am J Cardiol **20** 255 1967
11. Parry E H O and Abrahams, D G The natural history of endomyocardial fibrosis Q J Med. 36 383 1965
12. De Maria A N., Bommer W Newmann A Grehl, T Weinart L. De Nardo S., Amsterdam E A. and Mason D T Left ventricular thrombi identified by cross-sectional echocardiography Ann Intern Med, 90 14 1979

Echocardiographic diagnosis of left ventricular thrombi

Patricia C Come M D
John E Markis M D
Hugh S Vine M D
Barry Sacks M D
Colin McArdle M D
Alberto Ramirez M D
Boston Mass

Although left ventricular thrombi are frequently found at postmortem examination and can be identified angiographically[3] in many patients with cardiovascular disease they have only recently been identified by echocardiographic techniques [9] Reports of their recognition are still few and the M mode and cross sectional echocardiographic appearances of the clots have been variable Presented below are two patients with left ventricular thrombi recognized echocardiographically and documented by pathologic and/or angiographic examination whose M mode and cross sectional echocardiograms add to the spectrum of echocardiographically detectable ventricular clot The sensitivity and specificity of echocardiographic techniques in the diagnosis of intracardiac thrombi are discussed

Methods

The M mode and cross sectional echocardiographic studies in each patient were performed with the patient s chest elevated 15 degrees and with the patient turned 30 degrees into a left lateral position

M mode echocardiograms were obtained using an Irex 101 or System II Ultrasonoscope coupled with a 2 25 MHz transducer focused at 7 5 cm They were recorded on an Irex System II recorder The echocardiographic transducer was placed along the left sternal border in the third or fourth intercostal space and was angled inferiorly and laterally to record echoes from the left ventricle An attempt was made to scan toward the apex

Cross sectional echocardiographic scans were obtained in multiple planes using the 80 degree Varian Model 3000 Phased Array Sector Scanner A long axis view of the heart approximating a sagittal plane was obtained by positioning the transducer in the third or fourth intercostal space to the left of the sternum and directing the plane of the sweep from the inferior wall of the left ventricle to the base of the heart An attempt was made in each patient to visualize the apex in the sagittal plane by placing the transducer at the position of the apical impulse and directing the plane of the sweep superiorly and inferiorly Such a change in transducer position is necessary for visualization of the left ventricular apex in the sagittal plane since in most patients an echocardiographic scan from the apex to the base of the heart involves changing the plane of the echocardiographic sweep Short axis (transverse) views of the left ventricle were obtained by positioning the transducer along the left sternal border or at the apex (for a transverse view of the apex) and directing the plane of the sweep perpendicularly to the long axis of the heart along an imaginary line connecting the left shoulder and the right hip Four chambered views from the apex were

From th Thorndik Laboratory nd Comb ned Echocard ogr phic Service f th Dep rtments of Med cine and Rad ology Beth Israel Hospital Departm nt of Medicin Faulkn r Hosp tal a d Harvard Medical School, Bost n Mass.

Received fo p blication Jun 7 19 9
Accepted fo publication Aug. 1 1979

Reprint requests P tricia C Com M D D pt. of Medicine Card o-vascular Division, Beth Isra l Hosp tal, 330 Brooklin Ave Bost n MA 02?15

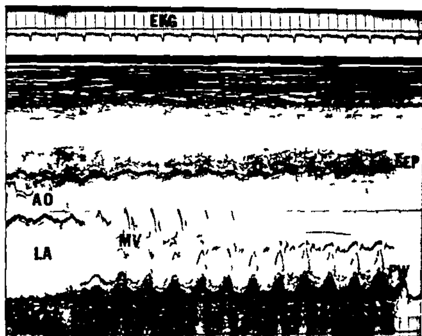


Fig 3 M mode echocardiographic scan from the aortic root (*AO*) and left atrium (*LA*) to the left ventricle in Patient No 1 after removal of 78 grams of left ventricular thrombus The left ventricle remains enlarged. The septum (*SEP*) is dyskinetic *MV* = mitral valve *PW* = posterior left ventricular wall *EKG* = electrocardiogram

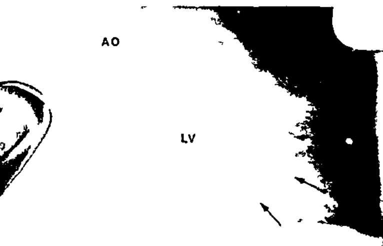


Fig 4 Left ventriculogram in the right anterior oblique projection in Patient No 2 Angiographic dye fails to fill the entire left ventricle due to the presence of a large apical mural thrombus which appears to be adherent to the left ventricular wall *Arrows* demonstrate the border between dye and mural thrombus *AO* = aortic root *LV* = left ventricular cavity

wall moved well and because the thrombus appeared to be confined to the apex on cineangiographic study It is perhaps more likely that the band of echoes represented an echo producing pericardial effusion with adhesions between epicardium and pericardium resulting in movement of the pericardium If so failure to identify thrombus by M mode echocardiographic tech nique may have been due to the inability to sca down into the apical region On cross sectiona echocardiographic examination a well-define echocardiographic density was observed adjacen to and moving with the ventricular apex N pericardial effusion was apparent Angiograph findings were diagnostic of a left ventricula thrombus which appeared firmly adherent to th apical wall

Although left atrial and left ventricular throm bi are found far more frequently at postmortem examination than are primary or secondary intra cardiac tumors[1] [11,13] reports of their recogni tion by echocardiographic techniques have bee relatively few[9,11,13] compared to multiple reports of echo diagnosis of intracardiac neoplasms[1,3] In a study by Ports and associates' of e patients with surgically proven left ventricul thrombi none were detected by M mode echoca diography and only the four largest thrombi we detected by cross sectional techniques. In anoth er study by DeMaria and co workers cross sectional echocardiography detected den ties compatible with apical thrombus in five patien who experienced peripheral emboli follow myocardial infarction The M mode echocard grams in those patients revealed no signs of thrombi The ability of echocardiographic tech

areas of firm white tissue thought to represent focal organization The right and left brachial artery emboli were identified as recent thrombus.

Postoperative M mode echocardiography (Fig 3) revealed *disappearance of the previously noted intraventricular echoes.* The patient made a satisfactory recovery and was discharged on the sixteenth postoperative day on digoxin and sodium warfarin Ventricular ectopy was markedly diminished on no medications. Following discharge however progressive severe congestive heart failure developed and the patient died seven months after surgery

Case report No 2

P D a 3? year old man with a history of anterolateral transmural myocardial infarction four months previously was admitted to Beth Israel Hospital for cardiac catheterization to evaluate post myocardial infarction angina pectoris. Medications included propranolol and nitrates.

On physical examination the pulse was 80 and regular the blood pressure was 130/80 mm Hg and the weight was 238 pounds There was no evidence of jugular venous distension rales, murmurs or gallops The electrocardiogram revealed changes of an old anterolateral myocardial infarction The chest x ray was normal, without cardiomegaly or evidence of failure Cardiac catheterization revealed an elevated left ventricular filling pressure of 17 mm Hg a cardiac index of 2 6 liters per minute and an ejection fraction of 44% The left ventricle was dilated and there was paradoxical motion of the anterior wall and apex A large apical left ventricular filling defect was present and appeared to be adherent to the left ventricular myocardium (Fig 4) The right coronary artery was occluded proximal to the crux. The left coronary artery had diffuse irregularities but no apparent critical stenosis. Surgery was not recommended

M mode and cross sectional echocardiography were performed following cardiac catheterization. The M mode echocardiogram (Fig 5) revealed a markedly dilated left ventricle measuring 8.2 cm in diameter The septum which measured 11 mm in thickness in end-diastole moved paradoxically and failed to *thicken with systole The posterior wall demon*strated normal systolic motion but there were multiple echoes from the posterior wall of the heart measuring 22 mm in end-diastole The cross sectional long axis and four-chambered apical views (Fig 6) demonstrated an intraventricular mass adherent to the left ventricular apex The mass was well defined and both it and the underlying myocardium moved dyskinetically There was no apparent pericardial effusion on the cross-sectional views

Discussion

The echocardiographic appearances of intracardiac thrombi are variable [11 3] Left atrial thrombi have been recognized by abnormal linear densities or by masses of echoes within the left atrium [8 11 3] The appearances of left ventricular thrombi have ranged from fine dust like densities [3] to more discrete clusters or bands of echoes adherent to the septum or occupying the apical region of the left ventricular cavity [6] The echocardiographic findings in our two patients add to the reported spectrum of appearance of intracardiac thrombi In the first patient a dense mobile mass of echoes was seen to partially fill the left ventricular cavity and appeared during systole to move into the left ventricular outflow tract There was no apparent connection of this mass to the left ventricular wall on either M mode or cross sectional echocardiographic examination The movement pattern of the mass seen well on the cross sectional study would make differentiation from a mobile intraventricular neoplasm such as a ventricular myxoma impossible In the second patient it is unlikely that the M mode echocardiographic appearance of abnormal thickness of the posterior wall represented thrombus adjacent to myocardium because the posterior

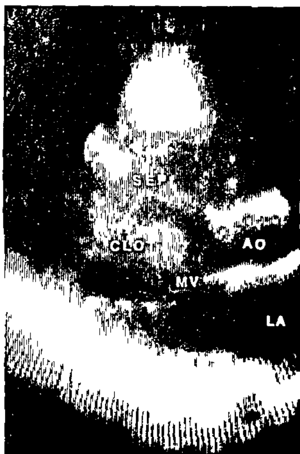


Fig 2 Preoperative cross sectional recording of the heart in Patient No 1 A dense mass of echoes representing the surgically confirmed clot, is seen to fill much of the left ventricular cavity during diastole The mass appeared freely mobile and without obvious attachment to the septum (*SEP*) or mitral valve leaflets (*MV*) During systole the echogenic mass was seen to move further into the left ventricular outflow tract *AO* = aortic root *LA* = left atrium

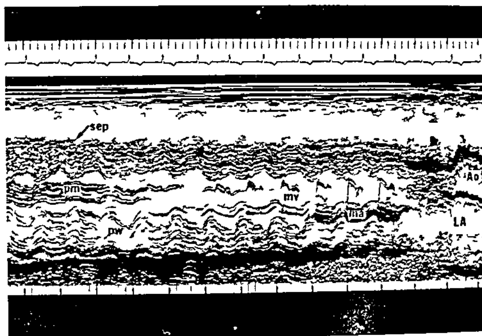


Fig 7 Slow scan from the apex of the left ventricle to the aortic root (*AO*) and left atrium (*LA*) in a hypertensive patient with severe concentric hypertrophy of the septum (*SEP*) and posterior wall (*PW*) A thick dense band of echoes representing a hypertrophied papillary muscle (*PM*) is seen within the left ventricular cavity *MV* = mitral valve *MA* = mitral annulus

metastatic neoplasms may produce echocardiographic patterns similar to thrombus Normal intracardiac structures which have become thickened or calcified may cause abnormal echoes within the left ventricular cavity Due to failure of lateral resolution a calcified mitral valve annulus may on M mode or cross sectional echocardiographic study appear to extend inferiorly into the left ventricular cavity[3] Calcified chordae or papillary muscles[1] may give the appearance of a dense intraventricular mass In such cases cross sectional echocardiography may help to clarify the origin of abnormal echoes seen on M mode study because it allows better recognition of anatomic relationships and movement of structures relative to one another This is illustrated by the recent study in our laboratory of a 32 year old woman with a long history of hypertension and left ventricular hypertrophy Severe concentric left ventricular hypertrophy was noted on the echocardiographic studies with septum and posterior wall both measuring 23 mm The mitral annulus appeared calcified With scanning inferolaterally toward the left ventricular apex on M mode echocardiography (Fig 7) a dense mass of echoes similar to that seen in patient No 1 was observed to partially fill the left ventricular cavity On one dimensional examination those echoes appeared to be separate from septum and posterior wall However the two dimensional echocardiogram revealed that the abnormal mass of echoes represented papillary muscle continuous inferiorly with the apical ventricular wall and superiorly with chordae giving support to the mitral valve leaflets (Fig 8)

The cases presented serve to further illustrate the variable echocardiographic appearances of left ventricular thrombi and emphasize the potential difficulties of differentiating them from other intracardiac structures or mass lesions Strict attention to echocardiographic technique may improve the sensitivity of echocardiography in the detection of left ventricular thrombus Since thrombus is located most commonly in the left ventricular apex[3] an attempt must be made to scan inferiorly and laterally toward the apical region on M mode examination A slow sweep from the apex to the base of the heart may allow recognition of focal wall thickening which may be produced by overlying mural thrombus The use of multiple cross sectional views such as the long and short axis views with the transducer placed at the apex and the four chambered apical view[1] should allow optimal study of the apex and improve the sensitivity of cross sectional echocardiography in the detection of thrombi

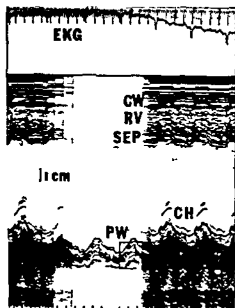


Fig 5 M mode echocardiographic recording from Patient No 2 shows a dilated left ventricle The septum (SEP) move paradoxically and fails to thicken during systole compatible with prior infarction Multiple echoes (PW) measuring 22 mm in width at the end of diastole are recorded from the region of the posterior wall and pericardium EKG = electrocardiogram CW = chest wall RV = right ventricle CH = chordae 1 cm = one centimeter

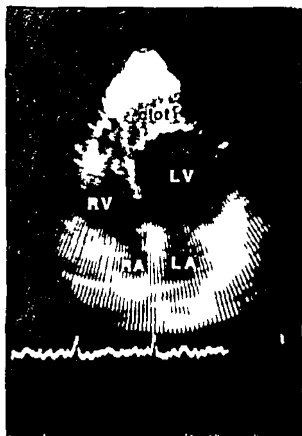


Fig 6 Cross sectional echocardiographic recording of the four-chambered apical view in Patient No 2 shows a large echogenic mass adherent to the ventricular wall and filling the apex (clot) LV = left ventricle LA = left atrium RV = right ventricle RA = right atrium. The electrocardiogram is below the echo

niques to identify thrombi is probably limited by several factors First the thrombus may be too small to be recognized Secondly the echocardiogram will be unable to record echoes from a thrombus if the sound beam is not directed toward the mass Since many left atrial thrombi are located within the atrial appendage a part of the heart not visualized by routine echocardiographic scanning recognition of those intra atrial thrombi by usual echocardiographic techniques is not possible Most left ventricular thrombi are located in the apex of the left ventricle[3] and will not be visualized unless the beam can be directed toward the apex The apparent increased sensitivity of cross sectional echocardiography over M mode echocardiography in the recognition of left ventricular masses[5] is probably in part due to the ability of cross sectional techniques to visualize many more regions of the heart particularly if multiple echocardiographic planes are examined Finally the difference in acoustic impedance of blood and thrombus or of ventricular wall and thrombus may be insufficient for adequate reflection of sound waves at their interfaces Ports and colleagues[3] noted that those thrombi recognized echocardiographically had layers of organized thrombus alternating with areas of more recent thrombus formation In the first patient presented above the thrombus seen readily by echo techniques as a dense mass of echoes also contained areas of fresh thrombus as well as areas of organized thrombus If such inhomogeneity is associated with differences in acoustic impedance such layered thrombi may produce sufficient reflection of ultrasound to allow their recognition This is likely since it is known that the reflection characteristics of body tissues are in large part dependent on their content of collagenous fibers

Unfortunately echocardiographic patterns suggestive of thrombus may not be specific Variations in gain and reject settings and reverberations may produce spurious echoes within an intracardiac chamber Intracardiac primary and

of atrial tumors by ultrasound Circulation 39 615 1969

19 Finegan R. E and Harrison D C Diagnosis of left atrial myxoma by echocardiography N Engl J Med 282 1022 1970

20 Nasser W K., Davis R H., Dillon J C Travel, M E., Helman C H Feigenbaum H., and Fisch C Atrial myxoma. II Phonocardiographic echocardiographic hemodynamic and angiographic features in nine cases AM HEART J 83 810 1972

21 Martinez E C Giles T D., and Burch G E Echocardiographic diagnosis of left atrial myxoma Am J Cardiol. 33 281 1974

22 DeMaria A. N Vismara L. A Miller R R., Neumann A and Mason D T Unusual echographic manifestations of right and left heart myxomas Am J Med 59 713 1975

23 Harbold N B., Jr., and Gau G T Echocardiographic diagnosis of right atrial myxoma Mayo Clin Proc 48 284 1973

24 Goldschlager A., Popper R Goldschlager N Gerbode F., and Prozan G Right atrial myxoma with right to left shunt and polycythemia presenting as congenital heart disease Am J Cardiol 30 82 1972

25 Meyers S N., Shapiro J E Barresi V DeBoer A A., Pavel D I., Gracey D R., Suhre D E and Buehler J H Right atrial myxoma with right to left shunting and mitral valve prolapse Am. J Med. 62.308, 19[illegible]

26 Morgan D L. Palazola J Reed W Bell, H F Kindred L. H and Beuchamp G D Left heart myxomas, Am J Cardiol 40 611 1977

27 Dashkoff N., Boersma, R B Nanda, N C Gramiak, R. Andersen M N and Subramanian, S. Bilateral atrial myxomas. Echocardiographic considerations, Am. J Med. 65 361 1978

28 Lappe D L., Bulkley B H., and Weiss, J L. Two-dimensional echocardiographic diagnosis of left atrial myxoma, Chest 74 55 1978

29 Kerber R E Kelly D H., and Gutenkauf C. H. Left atrial myxoma. Demonstration by stop-action cardiac ultrasonography Am J Cardiol. 34 838 19[illegible]

30 Farooki, Z. Q Henry J G Arciniegas, E., and Green, E W.. Ultrasonic pattern of ventricular rhabdomyoma in two infants, Am. J Cardiol. 34 842, 19[illegible]

31 Fields S and Dunn F Correlation of echographic visualizability of tissue with biological composition and physiological state J Acoustical Soc Am. 54 [illegible] 1973

32 Dashkoff N., Karacuschansky M., Come P C., and Fortuin N J Echocardiographic features of mitral annulus calcification AM HEART J 94 585, 19[illegible]

Since the echocardiographic patterns are not specific for thrombus however other possibilities must be considered when an abnormal mass of echoes is demonstrated Those would include artifacts primary or metastatic tumors and normal intracardiac structures which have become more intensely echo producing due to alterations in their size anatomic position within the heart or acoustic impedance properties

Summary

Left ventricular thrombi have not been commonly recognized by M mode or by cross sectional echocardiographic techniques despite their frequency at postmortem examination in patients dying of cardiovascular disease We discuss two patients with left ventricular thrombi recognized echocardiographically and confirmed by pathologic and/or angiographic evaluation whose M mode and cross sectional echocardiographic abnormalities add to the variable spectrum of appearance of left ventricular thrombi The sensitivity and specificity of echocardiographic techniques in the diagnosis of intracardiac thrombi are discussed



Fig 8 Cross-sectional long axis, diastolic view of the heart in the patient with left ventricular hypertrophy demonstrates the severe thickening of the septum (*VS*) posterior wall (*PW*) and papillary muscle (*PM*) The *tip of the arrow* points to chordal attachments between the anterior leaflet of the mitral valve and the papillary muscle A calcified mitral annulus is seen below the *base of the arrow* *AO* = aortic root *LA* = left atrium The electrocardiogram is below the echo

REFERENCES

1 Yater W M Welsh P P Stapleton J F and Clark M L Comparison of clinical and pathologic aspects of coronary artery disease in men of various age groups a study of 950 autopsied cases from the Armed Forces Institute of Pathology Ann Intern Med 34 352 1951
2 Garvin C F Mural thrombi in the heart AM HEART J 21 713 1941
3 Hamby R I Wisoff B G Davison E T and Hartstein M L Coronary artery disease and left ventricular mural thrombi clinical hemodynamic and angiocardiographic aspects Chest 66 488 1974
4 Horgan, J H Shiel F O M and Goodman B S Demonstration of left ventricular thrombus by conventional echocardiography J Clin Ultrasound 4 287 1976
5 Ports T A Cogan J Schiller N B and Rapaport E Echocardiography of left ventricular masses Circulation 58 528 1978
6 Kramer N E Rathod R Chawla K K Patel, R and Towne W D Echocardiographic diagnosis of left ventricular mural thrombi occurring in cardiomyopathy AM HEART J 96 381 1978
7 DeJoseph R L Shiroff R A., Levenson L W Martin C E and Zelis R F Echocardiographic diagnosis of intraventricular clot Chest 71 417 1977
8 Mikell, F Asinger R Rourke T Hodges M Sharma B and Francis G Detection of intracardiac thrombi by two-dimensional echocardiography (Abstr) Circulation 58(Suppl II) II-43 1978
9 DeMaria A N Bommer W Neumann A., Grehl, T Weinart L., Denardo S Amsterdam E A and Mason D T Left ventricular thrombi identified by cross sectional echocardiography Ann Intern. Med 90 14 1979
10 Silverman N H and Schiller N B Apex echocardiography a two-dimensional technique for evaluating congenital heart disease Circulation 57 503 1978
11 Poehlmann H W Basta L. L., and Brown R E Left atrial thrombus detected by ultrasound—a case report J Clin Ultrasound 3 65 1975
12 Spangler R D and Okin J T Echocardiographic demonstration of a left atrial thrombus Chest 67 716 1975
13 Graboys, T B., Sloss L J and Dokene J A. Echocardiographic diagnosis of left atrial thrombus—a case report J Clin Ultrasound 5 284 1977
14 Pritchard R W Tumors of the heart Arch Pathol 51 98 1951
15 Leach, W B Primary neoplasms of the heart, Arch. Pathol 44 198 1947
16 Effert S and Domanig E The diagnosis of intra atrial tumors and thrombi by the ultrasonic echo method German Med. Mon. 4 1 1959
17 Popp R. L., and Harrison, D C Ultrasound for the diagnosis of atrial tumor Ann Intern Med 71 785 1969
18 Wolfe S B Popp R L and Feigenbaum, H Diagnosis

Table I Classification of interventions used to reduce indices of infarct size in patients or infarct size in animals

	Reduction of experimental infarct size	*Effect on indices of infarct size in patients*
1 Relief of vascular obstruction		
Antithrombotic agents	Heparin reduces tissue necrosis	Reduces ST segment elevation[14]
Antiplatelet agents	Aspirin does not alter thrombus	Not tested
Relief of spasm Ca antagonists	Complex action including increased collateral flow specific reduction of contractility in ischemic zone[2] and afterload reduction	Reduction of load on heart and of ST-elevation and reduction of predicted enzymatic infarct size in 9 of 11 patients
2. Increased collateral flow or diffusion to ischemic zone		
Nitrates	Increased collateral blood flow[4] [90]	See Tables V VIII and references 190-195
Hyaluronidase	Reduces QRS changes and necrosis	See Tables V VII and reference 206
Intra aortic counterpulsation	Reduces ischemic injury	Not tested but see reference 236
Surgical reperfusion	Data controversial see reference 2	Not tested
3 Relief of load on heart		
Nitrates (see also Section 2 Table I)	Reduces load[100] ST ↓ [90] [90] CK preservation[90]	ST ↓ with intravenous NG [95] for sublingual NG see references 191 19?
Nitroprusside	Controversial effects	Controversial effects on ST segment, see references 200 and 244
Other vasodilators		
Ca antagonists	Reduction of necrosis	Reduction of predicted infarct size
Diazoxide	No data	Increased ECG changes in 9 of ?0 patients
Ganglion blockade	For general effects of afterload reduction see reference 1	Trimethaphan reduces predicted infarct size
4 Catecholamine antagonists		
β blocking agents	ST ↓ CK preservation lessened necrosis	ST ↓ less CK release improved metabolism see Table II
α blocking agents (phentolamine)	Not documented	Only hemodynamic data[84]
5 Specific metabolic measures		
Increased provision of oxygen	Reduction of infarct size[2]	ST elevation ↓
Inhibition of fatty acid metabolism	Decreased enzyme release	ST elevation ↓
Glucose insulin potassium	Decreased necrosis improved metabolism[60]	Inotropic effect without CK effects[43]
Calcium antagonists	(see Relief of spasm)	(see above)
Prevention of severe cellular acidosis	Not fully tested may be effective	Not tested
Stabilization of membranes	Steroids reduce ischemic injury[58] and infarct size[50] with mummification[30]	Controversial effects reduce Q wave formation
Prevention of cell swelling	Mannitol reduces necrosis only after temporary ischemia[25] but not after prolonged occlusion	Not tested

series of fundamental papers in 1963 showed that pronethalol which lacked intrinsic sympathetic activity could relieve angina pectoris in patients with ischemic heart disease Pronethalol was soon superceded by propranolol which strangely had no apparent effect on angina in its first trial[13] although propranolol is now established as a major advance in the therapy of angina Many of the more recent studies are with the cardiospecific agent practolol which has a certain amount of intrinsic sympathetic activity but now cannot be used for long term therapy because of serious undesirable side effects Of the large number of β blocking agents currently available relatively few have been tested in patients with acute myocardial infarction (Table II) The more recent recognition that similar factors to those precipitating angina can act to increase ischemic damage in developing infarction (see Fig 1 Part 1) made it logical to search for effects of β blockade on infarct size

In view of the established effects of propranolol on heart rate and afterload reduction and the recently reported effects on collateral flow (see

Myocardial infarct size Part 2 Comparison of anti infarct effects of beta blockade glucose insulin-potassium nitrates and hyaluronidase

Lionel H Opie M D
Cape Town South Africa

Based on the principles discussed in the first part of this review the following interventions (Table I) could be expected to limit infarct size (1) relief of vascular obstruction (2) increased collateral flow or diffusion to the ischemic zone (3) relief of the load on the heart thereby promoting a more favorable balance between the oxygen supply and demand (4) catecholamine antagonism and (5) specific metabolic measures Table I lists those agents tested in patients for therapeutic effects on indices of infarct size Because the role and exact nature of the vascular obstruction is so controversial agents acting at that level have been omitted from further consideration and one agent has been selected from each of the remaining categories (2 to 5) of Table I

Thus the four anti infarct agents selected for consideration in further detail are β blockade glucose insulin potassium nitrates and hyaluronidase β blockade is selected because of the exceptionally full experimental and clinical studies now available and because of a combined hemodynamic and metabolic action Glucose insulin potassium is selected as one of the first interventions introduced and now well studied over many years it is an agent likely to counteract undesirable metabolic changes in acute infarction Glucose insulin potassium is compared with the use of a nicotinic acid analog which also has an antilipolytic action Nitrates are selected because of their dual mechanism of action both by causing coronary vasodilation and by reducing the pre and afterload on the heart In addition nitrates as therapeutic agents are well known to all practicing cardiologists Nitroprusside is considered together with the nitrates although nitroprusside has a more definitive effect on the afterload than do nitrates Finally hyaluronidase is chosen as a well investigated agent with minimal side effects and no known hemodynamic mode of action

Other promising agents have been omitted although of great potential interest because of the limited number of patient studies available For example the effects of *steroids* are well documented in experimental preparations Although they diminish the features of acute ischemic injury probably acting by means of membrane stabilization they also inhibit wound healing and hence increase the risk of ventricular rupture or aneurysm (See also Table I references 250 251 256 and 257) Another interesting category of agents the calcium antagonists are only now being studied in patients

1 β blockade

Effects of propranolol on ischemia Black in 1957 searched for a compound to improve ischemia by reducing the effects of sympathetic stimulation and decreasing the myocardial oxygen demand [3] The dichloro analog of isoproterenol was the first compound found to inhibit the adrenergic receptors of the heart but the marked stimulant effect on the heart rate (intrinsic sympathetic activity) obviously limited the therapeutic potential of this type of compound.[3] A

From the MRC Ischemic Heart Disease Research Unit, Department of Medicine Groote Schuur Hospital and University of Cape Town Cape Town South Africa.

Received for publication Dec. 29 1978

Reprint requests Dr Lionel H Opie Dept of Medicine Medical School, Observatory 7925 Cape, South Africa.

0002-8703/80/100531 + 2 $00 20/0 1980 The C V Mosby Co

Table III Contraindications to β blockade used in various studies

Parameter	Definition	Author
1 Heart failure	Clinical	
	Cardiomegaly	Mueller et al
	Severe dyspnea	Waagstein and Hjalmarson
	Crepitations 3rd heart sound venous pressure exceeding 3 cm above sternal angle	Barber et al.
	Signs of poor peripheral circulation—eg., coldness or pallor	Waagstein and Hjalmarson
	Cardiac index < 2.5	Gold et al.
	Radiological	Peter et al.
	Interstitial edema or pulmonary edema but pulmonary venous congestion accepted	
2. Hypotension	Systolic cuff pressure	Mueller et al.
	110 mm. Hg	
	< 100 mm. Hg	Waagstein and Hjalmarson
	Mean arterial pressure	
	< 75 mm. Hg	Gold et al.
3 Bradycardia	Rate below 80/min	Gold et al.
	Rate below 65/min	Mueller et al.
	Rate below 60/min	Peter et al.
	Rate below 45/min.	Waagstein and Hjalmarson
4. Conduction defects	No AV block	Mueller et al.
	AV block exceeding first-degree	Peter et al.
	QRS duration not more than 100 msec.	Waagstein and Hjalmarson
5 Lung disease	History of chronic lung disease or asthma for propranolol	Mueller et al.
6. Age	Over 65 excluded for propranolol	Peter et al.

The β blocking agents used are (a) Propranolol, (b) Practolol or metoprolol (c) Practolol.

changes and the metabolic effects of β blockade are of much interest Opie and Thomas found that propranolol pretreatment reduced considerably the uptake of free fatty acid by the ischemic zone of coronary ligated dog hearts while the uptake of glucose was correspondingly increased Their findings are in agreement with the increased respiratory quotient of the heart in patients given propranolol[140] The net metabolic effect was a change from the metabolism of free fatty acids to that of glucose with a decreased oxygen uptake

It is not possible at present to clearly decide whether it is the metabolic or the hemodynamic effects of β blockade which are of greatest importance In patients substantial decreases in precordial ST segment elevation could be obtained by practolol even in those patients in whom the heart rate did not fall But if the metabolic effects on fatty acids were of importance then drugs such as propranolol, oxprenolol and acebutolol which are antilipolytic should be considerably more effective than drugs such as metoprolol which are not antilipolytic[144] Proof of such distinctions is still awaited

In summary most experimental evidence shows that β blockade causes myocardial mechanical metabolic and blood flow effects which are favorable to the outcome of developing myocardial infarction

Propranolol in patients with acute myocardial infarction In patients with acute myocardial infarction (Table II) Gold and associates recently reported that intravenous propranolol given to 12 selected patients caused an abrupt decrease in the ST segment elevation and decreased the incidence of arrhythmias. There were also substantial reductions in the arterial pressure the heart rate and the cardiac output but perhaps surprisingly heart failure did not develop as indicated by the pulmonary capillary wedge pressure which remained unchanged. In another important study, Mueller and co-workers showed that although the myocardial oxygen consumption per beat was decreased by intravenous propranolol and the myocardial blood flow was slightly reduced nevertheless lactate metabolism improved

These effects of propranolol on ischemic myocardium in patients have not yet been matched by studies with measurements of infarct size apart from the study of Peter and colleagues on highly selected patients. That study found decreased release of creatine kinase which was, however evident only

Table II β blocking agents used in patients with the clinical syndrome of acute myocardial infarction recent studies

Authors	*Agent*	*Route and dose*	*When given*	*Result*
Mueller et al	Propranolol	0 1 mg /kg in 3 divided doses at 5 minute intervals	6-8 hours after admission for acute transmural myocardial infarction (including inferior infarction)	Improved myocardial metabolism slight rise (2 mm Hg) in pulmonary wedge pressure
Gold et al.	Propranolol	I V 0 15 mg /kg	Anterior myocardial infarction within 8 hours of onset with persistent pain	Cardiac output fell but pulmonary wedge pressure did not rise ventricular irritability decreased decreased ST-elevation
Peter et al.	Propranolol	I V 0 1 mg /kg over 10 min followed by 320 mg over next 27 hours	Within 12 hours of onset of typical ischemic chest pain with ECG evidence of ST-elevation or pathological Q waves	Decreased blood levels of creatine kinase if propranolol given within 4 hours of onset of symptoms
Pelides et al	Practolol	I V [illegible]0 mg	Up to 72 hours after onset of symptoms	Decrease of area and severity of ST elevation
Barber et al.	Practolol	Orally 300 mg b d	As soon as patient seen and then for [illegible] years	If initial heart rate exceeded 100 per min., mortality reduced at 3 months
Waagstein and Hjalmarson [15]	Practolol	I V 5-30 mg (mean = 18 mg)	In coronary care unit as soon as possible after arrival	1 Dramatic pain relief 2. Double product fell from 10 500 to 8,500 3 ST segment fell by 29%
Waagstein and Hjalmarson [15]	Metoprolol	I V 15 mg	In coronary care unit as soon as possible after arrival	Similar effects to practolol but lower heart rate
Mulholland and Pantridge	Sotalol	I V 10 mg plus atropine 0 6 mg I V	Before transport by ambulance	Prevention of tachycardia (110-1?0 per min) during movement by ambulance better than practolol
Devlin et al	Sotalol	I V 10 mg	Before transport by ambulance	Normal pre movement heart rate kept low
Heikkila and Nieminen	Pindolol	I V 0.2 mg	Within 15 hrs. of onset	Improves systolic wall motion by echocardiography

Double product = systolic BP × heart rate I V = intravenous.

below) it is not surprising that the majority of animal experimental work shows that propranolol can substantially reduce the extent of ischemic injury and of myocardial necrosis [3] [4] (see also Opie and Thomas [2]) although there is no ready explanation for one discordant study [6] in which propranolol in a high dose (5 mg /kg) had no effect That study is especially difficult to understand because the same group found that propranolol reduced enzyme release in patients with infarction (see Table II) Other studies [5] show that propranolol decreases the extent of enzyme depletion and the development of epicardial Q waves in the infarcting dog heart However a possible disadvantage of propranolol is the decreased coronary perfusion pressure which might explain why propranolol decreased the coronary flow in the ischemic zone of open-chest anesthetized dogs [4] [31] [8] The most recent information from closed chest conscious dogs [3] indicates that propranolol causes a favorable redistribution of the blood supply to the ischemic area important hemodynamic differences from open chest preparations are the greater decrease of heart rate in open chest dogs (higher pre propranolol rate) and the lesser cardiac dilatation following propranolol in closed chest dogs [39]

In patients flow to the ischemic zone cannot directly be measured but indirect evidence suggests that propranolol improves the coronary flow relative to the metabolic demand [10] Thus propranolol can be expected to have a beneficial effect on the infarcting myocardium unless there is heart failure when the heart can be expected to enlarge further as a result of decreased contractility

Metabolic effects of β blockade Tissue necrosis ultimately depends on cellular metabolic

practolol given to patients with an initial heart rate exceeding 100 per minute improved the short term prognosis (Table II) A high heart rate during movement by ambulance can be prevented by sotalol (10 mg intravenously alone or with atropine 0 6 mg)[153, 154] but an effect on ischemic injury was not proven A randomized study in other situations—e g patients without heart failure in Killip groups 1 and 2—with positive effects on mortality would be required before β blockade could be recommended in other situations

β blockade Summary The use of β blockade to limit ischemic damage in acute myocardial infarction has extensive experimental and clinical support One report suggests that infarct size is limited in patients as shown by decreased rates of release of creatine kinase Certain contraindications require strict observation to avoid undesirable side effects Close monitoring of the patient is required Both mechanical and metabolic factors may account for the improvements observed There are insufficient data to recommend the general use of β blockade in patients with acute infarction

2 Metabolic interventions—Glucose insulin potassium (GIK)

GIK as a polarizing agent Although GIK is now known to have a metabolic action very similar to that of propranolol (compare Opie and Thomas[3] with Opie and Stubbs[1]) GIK was first popularized by Sodi Pallares and his group[1] as a polarizing agent that could restore K loss from the ischemic zone and hence improve mitochondrial function Their claim of improved K in the ischemic zone after experimental coronary occlusion has been questioned by Surawicz[1] but there is no real reason to doubt that K uptake can occur[6, 7] and that tissue K can improve Sodi Pallares work led to the expectation that GIK could reduce arrhythmias in patients with acute infarction but numerous contradictory studies were conducted before the recent description of the natural history of arrhythmias in acute myocardial infarction led to the knowledge that by far the majority of lethal ventricular arrhythmias (fibrillation) occur within the first 5 hours of the onset of symptoms[3] —i e before GIK was instituted in those studies The antiarrhythmic effects of GIK have now been shown by Lown s group[1] who found that GIK elevated the ventricular fibrillation threshold in dogs

Metabolic effects of GIK More recently [illegible] studies have shown that GIK can inhibit myocardial necrosis[1] as effectively as other anti inf[illegible] agents such as hyaluronidase[1] In the babo[illegible] GIK helps to minimize ischemic tissue metab[illegible] changes such as depletion of high energy phosphate compounds and of glycogen[161] Opie a[illegible] Owen[60] studied the metabolic effects of GIK [illegible] found that it was especially effective on th[illegible] border zone of the developing infarct when g[illegible] for 6 hours after coronary artery ligation How[illegible] er it was also striking that GIK increased glycogen in all infarct zones and according to s[illegible] workers the ultimate degree of necrosis is ver[illegible] closely linked to the degree of cardiac glycog[illegible] retention[135] Thus it may be that when given ov[illegible] a longer period than 6 hours GIK is able t[illegible] protect all zones against developing infarction I[illegible] should be stressed that GIK did *not* cause [illegible] accumulation of lactate or protons in th[illegible] ischemic tissue[161] in spite of the theoretical h[illegible]ard of this supposed side effect[16]

The cellular metabolic effects of GIK in dev[illegible]oping infarction were as follows[60] The extracti[illegible] of glucose increased relative to that of free fat[illegible] acid cardiac glycogen increased and there was a switch from the metabolism of free fatty acid to that of glucose with decreased ST segment eleva[illegible]tion similar metabolic effects can be achieved by propranolol in dogs[13] and in man[1]

To measure the maximal possible degree of conservation of oxygen induced by glucose in[illegible]lin potassium we examined GIK effects on a isolated perfused rat heart preparation (Table IV) After coronary artery ligation the extent of the ischemic zone was measured by a suprav[illegible] dye and by the severity of enzyme release Cha[illegible]ing the perfusate from a low potassium (3 0 mM) fatty acid solution to the addition of glucose insulin potassium (K = 5 9 mM) greatly d[illegible]creased the release of enzyme and the appar[illegible] size of the ischemic zone while the mechanical efficiency (measured as joules/ml oxygen utili[illegible]tion) was increased Thus compared with [illegible] fatty acid utilization at a low perfusate K GI[illegible] markedly spared oxygen by improving effici[illegible] by 60% Similarly excess FFA caused a [illegible] deterioration of efficiency in nonischemic [illegible]lated pig hearts[163] Although these data are n[illegible] necessarily applicable to the more complex [illegible] bolic situation in patients[1] yet the principle of [illegible]bolic situation in patients yet the principle of metabolic oxygen wastage" and mechanical inefficiency is stressed

when propranolol was given within 4 hours of the onset of symptoms and even then was of borderline significance ($P < 0.05$ $2P < 0.1$—usually it is the two tailed value for P which is quoted)

β blocking agents other than propranolol (Table II) Patient studies with β blocking agents other than propranolol are also shown in Table II and again the beneficial effects are apparent but again data on infarct size are missing The agent best researched in man practolol reduces pain ST elevation and short term mortality in patients with an initial heart rate exceeding 100 per minute [45] when practolol is started at a dose of 300 mg every 12 hours within 3 hours (median value) of the onset of symptoms Although practolol has undesirable side effects with long term usage there would appear to be no reason why short term practolol should not be used to institute treatment to be followed by another β blocking agent Another cardiospecific β blocker metoprolol also reduces pain and ST elevation when given *intravenously in the early stages* of myocardial infarction (see Table II)

The long term beneficial effect of β blockade in reducing sudden death after anterior myocardial infarction has been shown for practolol[48] similar data exist for alprenolol[49] which like practolol possesses intrinsic sympathetic activity But in neither study could the long term effects be ascribed to reduction of infarct size because the β blockade was started after the acute phase was over Theoretically it is incorrect to extrapolate from results obtained with practolol to results that might be expected with another β blocking agent such as propranolol which has no intrinsic sympathetic activity It remains possible that the presence and amount of intrinsic sympathetic activity is important in secondary prevention and it could be argued that only agents with such activity should be used for situations in which practolol has proved effective Other agents with intrinsic activity include oxprenolol pindolol alprenolol and acebutolol but the amount of intrinsic activity varies Because of the different properties of different β blocking agents it has been argued that it is unethical to promote drugs other than the tested ones (practolol alprenolol) for post infarct protection and the same arguments should hold for the acute phase

Sowton and associates and Shanks [31] have argued that it is the β blocking qualities which are of most importance and that additional qualities are of no real therapeutic significance Although many clinicians seem to feel that the use of agents with intrinsic sympathetic activity *in acute myocardial infarction leads to fewer* problems with bradycardia documentation of this theoretically possible view is not yet available Very recently a challenging research report suggests that dimethylpropranolol an agent without β blocking activity can protect against ischemic reperfusion damage [15]

Contraindications to β blockade (Table III) Each of the above cited studies used certain definite contraindications as listed in Table III It is of interest that the majority of workers did not require monitoring by invasive procedures such as Swan Ganz catheterization or measurements of the cardiac index to assess whether beta blockade should be instituted or discontinued

β blockade Claims and counterclaims In brief β blockade given in the acute phase is claimed to counteract the manifestations of acute ischemia and to improve the short term prognosis in patients. Studies on the effects of infarct size in patients are not yet at hand *although the rate of* release of creatine kinase may be diminished by propranolol (P values borderline by one method of analysis) [1]

The major arguments against the use of β blockade therapy rest on the possible harmful side effects Occasional patients may develop high grade heart block requiring a pacemaker and the dangers of hypotension or heart failure also exist One of 95 patients treated by Peter and associates [5] required balloon counterpulsation for heart failure thought to be precipitated by propranolol Although these side effects are rare especially in closely monitored and carefully selected patients they are all too visible in comparison with the invisible effects of reduction of infarct size Whether such potential side effects of β blockade are real hazards, awaits further studies The decision whether or not to use β blockade in a given patient must depend largely on the skill and discretion of the attending physician and his views on the desirability of reduction of ischemic injury and (possibly) infarct size and on the status of the patient (Table III) In view of the harmful effect of a high heart rate on ischemia (see Fig 4 Part I) it is theoretically desirable to reduce a tachycardia not caused by heart failure or infection i.e an inappropriate tachycardia Support for this view stems from the observations of Barber and colleagues[1] that oral

electrical stimulation of the heart with acute coronary occlusion

However, recently Heng and colleagues[163] showed that when high blood glucose values of 400 to 600 mg/100 ml were maintained in patients with acute myocardial infarction infarct size failed to decrease which is not surprising because the high blood glucose must be acting as a positive inotropic agent[177] Thus, when GIK is given extreme hyperglycemia should be avoided unless the inotropic effect is specifically desired In patients Sodi Pallares[178] recommended blood glucose values of between 120 and 140 mg/100 ml but tolerated values between 70 and 160 mg/100 ml However higher values of an average of 286 mg/100 ml were accepted by Rogers and co workers[16]

GIK and infarct size The study of Heng and associates[163] is one of the only two studies that have measured infarct size The numbers studied by Heng and colleagues[163] were too few to permit any firm conclusions as also conceded by the authors Furthermore the time after the onset of symptoms and the infarct size were too variable to allow tight grouping of the patients A larger randomized trial assessing the effects of GIK, is now underway[180] and may give clearer guidance on the possible value of GIK in acute myocardial infarction Present indications are that GIK reduced circulating free fatty acids and both the incidence of ventricular premature systoles and ventricular tachycardia survival appeared to improve but enzymatically estimated infarct size did not change However the major rise of free fatty acids occurs in the first 6 to 8 hours of the onset of symptoms[79] thus only when GIK is given very early could oxygen sparing' be expected

GIK Claims and counterclaims Although one nonrandomized trial[16] strongly suggests that GIK may improve mortality rate in patients with infarction Heng and co workers[163] felt impelled to stop their much smaller trial However they did not consider that excess hyperglycemia (see above) could be adversely affecting the development of the infarction by increasing heart work (mean arterial pressure and pulmonary artery end-diastolic pressure increased) in their study In fact the data of Heng and associates[163] could be interpreted to show that GIK may be a useful agent when an inotropic agent is required which appears not to extend infarct size even this conclusion cannot be reached with certainty on the basis of the small numbers studied by Heng and colleagues[163] but it is in keeping with careful ly documented dog data[173] and with ventricular function studies in patients[181]

Another situation for which GIK should be considered is the presence of severe heart failure with a low sodium syndrome[18]

GIK was also reported as reducing the incidence of heart block in an uncontrolled study but the potassium in GIK can promote prolonged A V conduction in normal subjects at even normal potassium levels[184] Thus more observations are required on patients with heart block

GIK Summary GIK has attracted considerable attention as being one of the first anti infarct agents studied. Experimental evidence shows that GIK reduces infarct size GIK has some propranolol like effects on heart metabolism including oxygen conservation The majority of clinical studies have not been conducted in the light of modern knowledge of the natural history of arrhythmias and the patterns of development of infarct size occurring after the onset of acute myocardial infarction nor has the effect on infarct size been assessed in most studies in man The results of a randomized study now underway will give better guidance on the possible use of GIK in acute myocardial infarction GIK may have a place as an inotropic agent not increasing infarct size

3 Reduction of the load on the heart and increased collateral flow by nitrates

Nitrates coronary vasodilation vs load reduction Amyl nitrite was used at the end of the last century for relief of angina by Lauder Brunton, who noted the association of increased arterial pressure with the anginal attack and found that amyl nitrite relieved the pain and decreased the arterial pressure Many years later Robinson found that for a given patient the double product of heart rate and systolic pressure required for the production of angina was relatively constant He concluded that the advantage of the hypotensive action of nitrate outweighed its action in producing tachycardia Furthermore venodilation was held to be the cause of decreased left ventricular end-diastolic pressure[14] It is evident that apart from the tachycardia nitrates produce reduction of the preload and the afterload changes which should be conducive not only to

Electrocardiographic effects of GIK Two experiments published by Calva and colleagues[6] are of particular historical interest because they antedate the current interest in the epicardial electrocardiogram generated by the work of Maroko and Braunwald.[6] In the GIK treated heart in spite of the ST-elevation initially being greater the final Q wave formation was less.

GIK dosage Although Sodi Pallares has had extensive experience of GIK in patients neither his work nor the MRC trial[16] were conducted in conditions which are directly relevant to our modern knowledge of the development of acute myocardial infarction. Thus in the MRC trial the average time elapsed since the onset of symptoms and the start of the GIK infusion was 24 hours or more in nearly 90% of patients by which time infarct size may largely be fixed (although reinfarction can still occur); furthermore the doses used were low and the glucose was sometimes given orally and the insulin subcutaneously (see Table V). Rogers and associates[6] Thus the effects of intravenous GIK in the early phases of acute myocardial infarction require assessment. Rogers and co workers[6] have shown that GIK (given into the right atrium as 300 g glucose, 80 mEq potassium, and 50 units soluble insulin per liter at the rate of 1.5 ml/kg/hr) is very effective in bringing down circulating free fatty acids in patients. When GIK was given for 4 days it induced potassium gain and elevation of blood glucose. This investigating team noted a transient hyperkalemia in some instances[6] and also found that the pulmonary wedge pressure did not rise with GIK treatment. It would nevertheless be important to search for GIK effects on pulmonary capillary wedge pressure in patients with left ventricular failure. The problem of hyperkalemia would be avoided by a variable potassium infusion as recommended by Sodi Pallares and Ponce de Leon.[1]

GIK as an anti lipolytic intervention Thus reduction of plasma free fatty acids is an important effect of GIK (Table IV). Lipolysis can also be inhibited by a *nicotinic acid analog*. In pacing induced angina the degree of ST depression (but not the development of chest pain) was reduced as the circulating free fatty acids fell. This intervention also reduces acute ischemic injury in patients with infarction as judged by decreased precordial ST elevation and decreased arrhythmias.[1] However repetitive use of this agent throughout the first 24 hours of acute myocardial infarction cannot be recommended because the blood free fatty acid values rebound[1] unless high doses are used which cause significant side effects. In contrast GIK can consistently depress circulating free fatty acid values in patients with infarction without side effects or rebound.[6,1] In addition however both GIK[173] and addition of glucose[79] can achieve their effects in the presence of unchanged circulating free fatty acid levels showing that GIK acts not only as an antilipolytic agent but also by promotion of glucose metabolism in animal models.

Table IV GIK and efficiency of rat heart compared with effects of very high fatty acid low K perfusate (Opie and Bricknell unpublished data)

	Efficiency (Joules per ml O₂)	*Enzyme release (mU/g/hr)*
Hearts perfused with pathologically high fatty acid and low K, K = 3.0 mM	3.10 ± 0.09 (45)	33,058 ± 3,397 (14)
Hearts perfused with glucose and insulin, K = 5.9 mM	4.93 ± 0.09 (55)	6,699 ± 329 (7)
Change	+60%	−80%

Effects of changing from low K high fatty acid perfusate to GIK (as glucose 11 mM, insulin 2 mU/ml, K = 5.9 mM) in isolated perfused working rat heart with coronary ligation. Efficiency was measured by comparing the oxygen uptake with the work performance. Enzyme release was taken as an index of ischemic damage and was measured as release of lactate dehydrogenase from the coronary venous effluent. The mechanism of the altered efficiency induced by these extreme alterations of substrate (high fatty acid to GIK) is unknown but may include oxygen wasting. Note that as efficiency rises with GIK enzyme release is greatly decreased. Mean values ± SEM.

Danger of hyperglycemia Maroko and co workers found that hypertonic glucose by itself was nearly as effective as GIK in preventing necrosis after coronary occlusion in dogs. It is however important to note that the blood glucose concentration should not be allowed to rise to values which are too high. Sonnenblick and colleagues injected hypertonic glucose into dogs shortly after coronary artery ligation; the blood sugar rose to values of nearly 700 mg/100 ml while the contractility of the heart increased and the elevated end-diastolic pressure fell. The therapy reduced the incidence of ventricular premature beats and of ventricular fibrillation. The beneficial effect of hypertonic glucose on arrhythmias has been confirmed[17] in that intravenous glucose prevents the onset of ectopic beats after

Table V Mechanism of action of four anti infarct agents based on experimental data and/or clinical observations

	Heart rate	*BP*	*Contractility*	*Afterload*	*Metabolism*	*Microvascular damage*	*Blood flow*
Propranolol	↓	↓	↓	↓	Yes	Yes	Redistribution
GIK[b]	Small increase	No	↑	No	Yes	No data	Increases coronary and out flow in man
Nitrates	No	↓	No	↓	No data	No data	Yes
Hyaluronidase[d]	No	No	No	No	No data	No data	Yes

References
= 51 1.5 140 14? 209 = 60 159 163 167 180 = 50 194 197 = 206 207 208

nally drew attention to the beneficial hemodynamic effects of afterload reduction in patients with left ventricular failure and acute myocardial infarction[199] Experimentally nitroprusside is more potent than nitroglycerin in decreasing systemic arterial pressure but less potent in increasing collateral flow as assessed by the retrograde blood flow method[49] while nitroprusside actually reduced collateral flow as assessed by microspheres[200] The effects of nitroprusside on ST segment changes are controversial both in animals and in man (see Table I) unfavorable effects may reflect excess hypotension with reduction of post stenotic coronary flow (Table I including Ref 244) In patients nitroprusside is more effective than intravenous nitroglycerin in reducing the peripheral vascular resistance [1] and hence would probably be the agent of choice in a hypertensive crisis complicating acute myocardial infarction However the balance of experimental evidence suggests that nitrates are more effective than nitroprusside in maintaining flow to the ischemic myocardium [0] The comparable effects of nitroprusside and nitroglycerin on infarct size in patients with predominant arterial hypertension and infarction requires assessment

Nitrates claims and counterclaims Present evidence suggests that oral or sublingual nitrates are a desirable therapeutic agent to reduce myocardial ischemic damage in the presence of left ventricular failure or possibly hypertension In patients without severe left heart failure hypotension tachycardia and even bradycardia are possible and unpredictable side effects with sublingual nitroglycerin[91] the addition of phenylephrine to avoid hypertension in patients without heart failure is disputed[193] Such harmful side effects have not been reported with intravenous nitrates which can be given even in the absence of left ventricular failure[193] but require careful hemodynamic monitoring Thusfar sublingual nitrates have been reported to have only beneficial effects when given to patients with severe left ventricular failure or pulmonary edema[193] However much more knowledge is required about the effects of nitrates on indices of infarct size and mortality as opposed to effects on ischemic damage (ST elevation) and about the comparative effects of nitrate and nitroprusside therapy in patients with hypertension

Nitrates Summary Nitrates have a triple action reduction of preload coronary vasodilation and afterload reduction Substantial hemodynamic evidence shows the benefit of nitrates including sublingual nitroglycerin in patients with acute myocardial infarction complicated by left heart failure but controversy surrounds the use of sublingual nitrates in patients without evident left ventricular failure In comparison with nitroprusside nitrates cause a greater reduction of the preload and a more consistent increase of collateral flow to the ischemic zone but a lesser effect in afterload reduction Critical studies showing an effect of nitrates in reducing infarct size in patients are not yet available

4 Increased diffusion to ischemic zone by hyaluronidase

Hyaluronidase was one of the first agents described as improving the consequences of coronary artery occlusion[203] but its mode of action by improving collateral flow is still only presumed Its introduction into clinical therapy

amelioration of anginal pain but to reduction of myocardial infarct size

Recent evidence supports the hypothesis that nitroglycerin acts as a true coronary vasodilator in dog preparations Becker and colleagues[18] found a favorable redistribution of coronary flow to the more ischemic subendocardial regions Epstein s group[9] have shown that when nitro glycerin is given with methoxamine[9] to keep heart rate and mean arterial pressure constant then the collateral flow is substantially increased while Bache[189] found that nitroglycerin infusion could increase blood flow to the central ischemic zone but could not exclude a primary effect on the transmural pressure

Nitroglycerin and acute ischemic injury The work of Epstein and co workers[190] has shown that sublingual nitroglycerin when given to selected patients with acute myocardial infarction may reduce precordial ST elevation However sublin gual nitroglycerin can in some patients cause a serious fall in the arterial pressure[191] and the resultant reflex tachycardia could theoretically increase ST elevation These effects can largely be avoided by limiting the use of sublingual nitrates to patients with left heart failure[192] Thus in acute pulmonary edema repetitive sublingual nitroglycerin was strikingly effective when em ployed as sole therapy,[19, A] emphasizing that although nitroglycerin reduces the afterload a more significant effect is reduction of the pre load[18, B] Although the simultaneous administra tion of an α stimulant such as phenylephrine is claimed to reduce the harmful side effects of nitroglycerin in patients without left ventricular failure[1] others find that added phenylephrine is harmful[193] Hence sublingual nitrates should be restricted to those patients with left ventricular failure in whom the prime aim of therapy is relief of failure and in whom reduction of infarct size is only a secondary aim

But nitroglycerin by infusion reduces the arte rial pressure without a tachycardia but with a decreased left ventricular filling pressure and decreased precordial ST elevation[1] These bene ficial effects were also evident in patients without left ventricular failure suggesting that intrave nous nitroglycerin is a more desirable agent than is the sublingual form for the reduction of ischemic injury possibly because the intravenous route allows finer regulation of hemodynamic effects

Another promising route of administration of nitroglycerin is percutaneously A theoretical advantage of the ointment would be that if the blood pressure fell too much the agent could simply be wiped off the chest This simple proce dure must merit intensive investigation in acute myocardial infarction

Nitroglycerin and infarct size Thusfar neither experimental nor clinical studies have been reported on the effect of nitroglycerin on infarct size But in dogs given both nitroglycerin infusion and methoxamine (to prevent hypotension and tachycardia), creatine kinase depletion de creased[90] A preliminary clinical report sug gests that an infusion of nitroglycerin at 50 μg/minute could limit R wave fall and decrease mortality rate

Long acting nitrates Long acting nitrates have for long been thought to have no special advantage over the sublingual nitrate in the treatment of angina Recently the drug isosorbide dinitrate has been studied in patients with acute myocardial infarction[97] An immediate dose of 10 mg orally was followed by 20 mg 1 hour later Left ventricular filling pressure fell, but in those patients who had no left ventricular failure the cardiac output stayed the same or fell whereas in those patients with left ventricular failure (de fined as a left ventricular filling pressure exceed ing 20 mm. Hg) the cardiac output usually rose The effects were noted up to 9 hours after the control observation i.e up to 8 hours after the second dose of isosorbide dinitrate These workers did not assess infarct size but the hemodynamic changes reported for patients with left ventricular failure are those which could be expected to improve ischemic injury

Nitrates and coronary vasospasm Maseri and associates[4] have proposed an important role for coronary vasospasm in the production of angina One recent report[12] suggests that arterial spasm is present in nearly half the patients studied within 12 hours of the onset of symptoms of myocardial infarction Nitrates relieved the coronary vaso spasm which is a further argument for the evalu ation of nitrates as anti infarct agents For relief of vasospasm nitrates would require comparison with α blocking agents[1, 3] and calcium antago nists[110]

Nitrates versus nitroprusside The effects of nitrates may be compared with those of nitro prusside, the agent used in the work which origi

Table VI Effect of four anti infarct agents on various stages of experimental myocardial infarction

	Ischemic injury (ST elevation)	*Necrosis (Q formation or histology)*	*Wound healing*
Propranolol	Yes	Yes	No data
GIK	Yes	Yes [illegible]	Conflicting data
Nitrates	Yes	Preliminary data [illegible]	No data
Hyaluronidase	No data	Yes [illegible]	Yes

In patients the comparative efficacy of the four anti infarct agents can be assessed by their effects on pain relief the precordial electrocardiogram (ST-elevation or Q formation), mortality rate and long term post infarct prognosis (Table VII) β blockade is effective against the widest spectrum of features of acute myocardial infarction only effects on Q wave formation have not yet been shown (no data)

It is very important to note that only β blockade has thusfar been shown to influence mortality rate in patients with acute myocardial infarction and that the only data available are for practolol given in specific circumstances (given to patients with initial heart rate exceeding 100 beats per minute within a median value of 3 hours of onset see Barber et al [116]) Although there are strongly suggestive data for GIK [15] a randomized study is essential The general lack of data on the effects of anti infarct agents on mortality rate is not because such effects could not be expected but probably because of the large numbers of patients required to show reduced mortality rate

Harmful effects and contraindications Among the possible harmful effects of anti infarct agents are the provocation of heart failure hypotension tachycardia or fluid and electrolyte problems (Table VIII) Judged by these criteria hyaluronidase is the safest agent followed by GIK Any adverse effects of GIK should be greatly limited by modern technology which can give a bedside glucose and potassium reading within minutes Oral nitrates can cause hypotension and tachycardia β blockade can cause heart failure hypotension and heart block The exact incidence of these side effects will only become known in time but careful patient selection should minimize undesirable effects In selected conditions either nitrates or β blockade are safe the effects of combinations are unknown although the opposing effects on the heart [illegible] suggest the possibility of therapeutic combi[illegible] tion

Thus, after due consideration of the contra[illegible] cations β blockade can be used intravenou[illegible] a coronary care unit with appropriate mon[illegible] (oscilloscope and some would say a Swan Ga[illegible] catheter) provided that the drug is given slow[illegible] β blockade can be given orally in the hosp[illegible] outside of the coronary care unit The use of GI[illegible] requires monitoring of blood glucose and pota[illegible] sium values which can be done not only in [illegible] coronary care unit but also in the general hosp[illegible] setting The use of nitrates also requires hemod[illegible] namic monitoring in the coronary care u[illegible] However long acting oral nitrates could be gi[illegible] to patients in the general hospital if heart fa[illegible] were present Although hyaluronidase [illegible] appear to be an agent safe enough for use in t[illegible] coronary care unit or in the general hospital [illegible] even outside the hospital it is stressed that [illegible] use of anti infarct agents by physicians [illegible] seeing a patient outside the hospital still requ[illegible] clinical trial

6 Ideal heart rate and blood pressure

It is sometimes *inferred* that ischemic dam[illegible] has extended or regressed by measurements of [illegible] determinants of the myocardial oxygen up[illegible] The argument is as follows If the afterload [illegible] reduced oxygen uptake will fall and ische[illegible] injury will decrease Supposing that an interv[illegible] tion reduces the blood pressure from 160 to [illegible] mm Hg systolic and the heart rate from 110 [illegible] beats per minute then the double prod[illegible] halved the myocardial oxygen demand ma[illegible] halved and one could infer that there should [illegible] substantial reduction in ischemic injury [illegible] hence in the ultimate infarct size provided t[illegible] all other factors are equal

As far as *heart rate* is concerned this argu[illegible]

tics stems from the experimental observations of Maroko s group [2, 114] who have shown that hyaluronidase can reduce infarct size and can counter the development of the Q wave in dogs with coronary ligation Unexpectedly hyaluronidase is not effective in the pig model [65] which presumably reflects the necessity for a patent collateral circulation for the action of an anti infarct agent to be manifest [31] The pig is thought to have a poorly developed collateral circulation

Hyaluronidase is one of the few agents which has been shown to counter the electrocardiographic signs of necrosis in patients with anterior myocardial infarction of less than 8 hours duration by inhibition of loss of the R wave and formation of the Q wave In that study [69] hyaluronidase was given as 500 units/kilogram intravenously as a bolus every 6 hours for 48 hours After a negative intradermal test (100 units intradermally observed for 5 minutes) 46 treated patients were compared with 45 control patients Nine patients were excluded because of an allergic reaction i e 9/100 or 9% of patients Patients with QRS prolongation or left anterior hemiblock were excluded not because it was feared that hyaluronidase could adversely influence such cases but because the assessment of the ECG signs of evolving infarction might have been obscured If the effect of hyaluronidase on necrosis could be extrapolated from the changes induced in the QRS pattern of the precordial electrocardiogram as in the case of dogs with coronary occlusion [23] then the degree of reduction of necrosis by hyaluronidase was about 24% (comparing the evolution of ΣR over 7 days in control with treated patients) This may be considered disappointing compared with the 45% reduction of necrosis in dogs achieved by hyaluronidase The difference could be explained by the fact that some of the patients in the hyaluronidase trial probably did not have an adequate coronary collateral circulation and therefore would be less responsive to therapy

However the above study does not allow the firm recommendation to be made that hyaluronidase should be given to all patients seen early enough in the acute stage of myocardial infarction A further trial including those patients whose ECG changes did not allow them to be included in the first trial (e g patients with posterior infarction) with long term follow up is required before such a conclusion can be made

Mode of action of hyaluronidase Hyaluronidase increases coronary collateral flow [2, 7] prevents the reduction of coronary flow induced by ischemia and counteracts the formation of edema fluid as ischemia progresses [2, 4] It would seem that the combinations of hyaluronidase with other anti infarct measures warrants experimental assessment

Hyaluronidase Summary Hyaluronidase has been carefully studied in a wide range of experimental preparations and has been shown to reduce ECG features of necrosis in selected patients with acute myocardial infarction Thus far no undesirable side effects have been reported except for allergy Further clinical trials are required before a general recommendation for use of this agent can be made

5 Comparative effects of the four selected antiinfarct agents (Table V)

Mechanism of action The comparative mechanism of action of the four anti infarct agents selected in this review are shown in Table V Of the agents β blockade is the only one acting on all the following parameters heart rate blood pressure contractility metabolism and coronary blood flow In addition propranolol decreases microvascular damage [6] GIK improves the metabolism and in doses giving marked hyperglycemia increases indices of contractility while not extending infarct size Nitrates act chiefly by decreasing the load but also by a blood flow effect Hyaluronidase is the only agent with no known effect on the mechanical behavior of the heart Hyaluronidase is thought to act by improved blood flow and only secondarily by improved tissue metabolism

The four agents considered act differently on the three stages of development of the experimental infarct ischemic injury development of necrosis and wound healing (Table VI) All agents are effective against early ischemic injury as judged by effects on the degree of ST elevation on the epicardial electrocardiogram All agents are effective against necrosis as judged by Q wave formation on the epicardial ECG or by histology only hyaluronidase[115] and possibly GIK have been shown to accelerate wound healing [11] (but see Ahmed et al [73]) These experimental criteria do not allow conclusions as to which agent would be the most effective in limiting ultimate infarct size

approximations of changes in ischemic injury For more precise evaluations of the effects of anti infarct agents measurements of precordial ECG changes or enzyme release patterns would be required

7 Timing of intervention

A further critical point is to know when to intervene Table IX shows that some interventions can be effective as judged by ST segment criteria up to 72 hours after coronary occlusion or the onset of symptoms Most animal work has been done within hours of the onset of coronary occlusion with the exception of exaggeration of enzyme release by isoproterenol[74] However the interpretation of those data based on increased liberation of creatine kinase up to 72 hours after coronary occlusion in dogs must be regarded with some reserve because of the capacity of excess β stimulation to cause release of enzymes even from an apparently normal heart[14] Nevertheless Shillingford and his group[117] found that β blocking agents could decrease ST-elevation up to 72 hours after the onset of symptoms in patients with myocardial infarction (Table IX) suggesting a prolonged effect of β stimulation Increased urine catecholamine secretion values are found up to 4 days after the onset of symptoms in some patients[1] Pelides and associates[113] restudied three patients at increasing times after the onset of symptoms and although there was a decreasing effect at the second study nevertheless they still obtained a decreased ST elevation and decreased precordial area of ST elevation

However chronic therapy (started before the infarct developed) with β blockade in patients with acute infarction can decrease ST elevation without altering the rate of Q wave formation[1]

Some of the above data suggest that it would seem reasonable to intervene with β blockade up to 72 hours or with afterload reduction (nitrates trimethaphan) 8 to 14 hours after the onset of symptoms On the other hand the data showing favorable electrocardiographic effects on necrosis (assessed by QRS changes) of hyaluronidase in patients were obtained within 8 hours after the onset (mean 4 6 hours) An important finding with hyaluronidase (given to dogs as a single bolus) was that it had to be given within 6 hours after experimental coronary occlusion and it had no effect 9 hours after coronary occlusion[114] Similarly propranolol had to be given within 4 hours of the onset of symptoms to be effective reducing enzyme release[115] Practolol was give within 3 hours (median) of onset of symptoms b Barber and co workers[116] Selwyn and associa studied the rate of evolution of Q wave cha and found that complete development took 6 to 12 hours Thus from many points of vi interventions should ideally start within 6 ho of the onset of symptoms

Conclusions There is no unanimity on the timing of the interventions Some data sug that anti infarct agents could be given m hours after the onset of symptoms Clearly how ever the sooner after the onset of symptoms t therapy is given the better Data with propra lol and hyaluronidase suggest that a delay of 4 8 hours (respectively) is the maximum that can b tolerated

8 Anticipated effects of commonly used agents on ischemic injury of infarct size in patients

Among agents frequently used in the therap acute myocardial infarction are heparin an ox gen mask antiarrhythmic agents such as li caine and anti failure drugs such as digita diuretics and aminophylline and agents a pain such as morphine It may be that each these agents may influence ischemic injury a or infarct size

Heparin is frequently used in acute myocardi infarction for its supposed effects in preven venous thrombosis and possibly in stopping t formation of arterial thrombosis The b action has not been well documented but wo be logical if the actual coronary thrombo (when present) has a stuttering or delayed or as originally suggested by clinical work as originally suggested by clinical work Heparin recently confirmed experimentally Heparin d creases signs of ischemic injury and lessens th necrosis when given following coronary art ligation in the dog and decreases ST segme elevation in patients[16] Hence it would be log to test the effect on infarct size Howeve cautionary note is needed Since heparin incre blood free fatty acids this action must to so extent antagonize the antithrombotic and a platelet effects of heparin

Increased arterial oxygen receives support f its use because on 100% oxygen patients e denced decreased precordial ST segmental ele

ble VII Effect of four anti infarct agents on the features of acute myocardial infarction in man

	Pain	*ST-elevation*	*Q formation*	*CK infarct size*	*Mortality*	*Post infarct prognosis*
β blockade						
i Propranolol	Yes	Yes	—	Yes	—	—
ii Practolol	Yes	Yes	—	—	Yes	Yes
iii Metoprolol	Yes	Yes	—	—	—	—
GIK	—	Yes	—	No	Suggestive data	—
Nitrates	Yes (preliminary)	Yes	Yes (preliminary)	Yes (preliminary)	Preliminary data	—
Hyaluronidase[f]	—	—	Yes	—	—	—

udd n death ex l dmg inferior infarct mechanism prob blv does not in olv early anti infarct effect because practol l tarted after the acute phase myocardial infarction Note that oral practolol is no l ge v labl
(infarct si e = either rat of release of creatine kinase or actual calculation of inf t e
) = absence of d ta
ferences
= 51 140 145 = 146 147 148 235 = 235 = 157 165 1 0 180 = 190 196, 259 260 = 206

ppears to be valid In closed chest dogs the verity of ischemic injury as judged by ST evation was directly related to the heart rate ver the range 30 to 215 beats per minute[7] hereas an increased heart rate induced by atrial acing increased estimated infarct size in dogs by 0%[7] (For the possible effects of atropine in voiding the dangers of bradyarrhythmias see ection 8)

However as far as *blood pressure* is concerned he oxygen sparing effect of hypotension induced y hemorrhage appears to be outweighed by the armful effects of decreased coronary perfusion ressure[15] Hence it would follow that hypoten ion plus bradycardia requires atropine treat nent but bradycardia without hypotension or eart block does not require therapy The ideal ypotensive agents should therefore be those hat at the same time will decrease arterial ressure but also protect the ischemic myocar lium from underperfusion Both β blockade and itrates may do this by redistribution of blood low and vasodilation respectively Conversely in increased blood pressure increases ischemic njury and infarct size Even systolic blood pres ures of 150 to 165 mm Hg gave rise to infarcts bout one quarter larger than did pressures educed by about 30 to 40 mm Hg[3] although the se of computer predicted infarct sizes is open to some question

The *ideal blood pressure* in acute myocardial nfarction has not been determined but in the case of patients treated by intravenous proprano lol[140] the blood pressure could be reduced from an initial mean arterial pressure of 92 to only 76 mm Hg Similarly intravenous nitroglycerin could reduce blood pressure from a mean of 108 to 87 mm Hg[19] while ST segment elevation decreased Thus it seems as if patients with acute myocardial infarction can tolerate relatively low heart rates and blood pressures and that such values may beneficially influence ischemic injury and infarct size However blood pressure reduction achieved by agents such as nitroprusside and diazoxide which do not at the same time increase collateral flow need not always be beneficial but may be harmful[2 00 20 21]

The effects of increases in *heart rate or blood pressure have been compared* in patients with fixed coronary obstruction[2 3] Tachycardia was more harmful than hypertension as judged by increased chest pain and ST segment changes despite similar increases in myocardial oxygen consumption In the case of metabolically active agents such as GIK the heart rate and blood pressure cannot be used to assess any *oxygen sparing effect* nor can any metabolic effect of β blockade thus be assessed Nor can the effects of complex interactions in patients with left ventricular failure and/or dilated hearts be so assessed Indirect estimates of hemodynamic per formance also give no idea of the effects of hyaluronidase which does not influence hemody namic parameters Thus at present changes in the inferred indices of myocardial oxygen demand (heart rate blood pressure) can only give rough

Table IX Period of delay from onset of symptoms or coronary occlusion to intervention changing ischemic damage or infarct size

Intervention	*Period*	*Conditions*
A. *Decreasing ischemic damage*		
Nitroglycerin (IV)	Up to 21 hours (mean 8 hours)	After onset of symptoms in patients ST-changes
Practolol (IV)	5 72 hours (mean 31 hours)	Effect on precordial ST-elevation in patients
Practolol (IV) [1]	24 72 hours	Effect on pain in patients with acute myocardial infarction
B *Decreasing infarct size*		
Hyaluronidase	6 hours (9 hrs no effect)	Coronary occlusion in dogs
Propranolol	3 hours	Coronary occlusion in dogs
Propranolol	4 hours	Enzyme release in patients
GIK and propranolol [59]	3 hours	Coronary occlusion in dogs
Afterload reduction[a] (trimethaphan)	14 hours	After onset of symptoms in patients
C *Increasing infarct size*		
Isoprenolol	72 hours	Closed-chest dogs enzyme release
Digitalis	11 19 hours	After onset of symptoms enzyme release

A ganglion blocking agent
IV = intravenous administration

tion relief of pain and pulmonary edema should lead to decreased discharge of catecholamines [230] Although the possibility that morphine could cause arterial hypotension in some patients raises doubts about coronary perfusion the hypotensive effect appeared short lived and 15 minutes after the morphine baseline arterial values were regained [3]

Atropine when given for bradycardia, may avoid bradyarrhythmias which could increase infarct size by hypoperfusion On the other hand an atropine induced tachycardia could also increase infarct size The optimal lower limit of heart rate has not yet been defined

Commonly used agents Summary It is reassuring that many agents routinely used in the management of acute myocardial infarction are more likely to limit than to extend infarct size or ischemic injury with the exception of digitalis given to the nonfailing heart Aminophylline is probably harmful by provocation of arrhythmias

9 Can provisional guidelines to management of infarct size be given?

A distinction must be made between a general recommendation th t the time has not yet come to introduce anti inf r t agents into general cardiological prac ice nd recommendations for individual patients General recommendations could only be made once randomized trials have shown that relatively safe agents could decrease mortality rate or significantly change other complications of infarction That point has not been reached In the meantime the cardiologist faced with a patient with myocardial infarction needs to match existing data with the desire to do the best for the individual patient

Because it has been shown that larger infarcts are on the whole associated with a worse prognosis it would seem only prudent to avoid agents known or suspected of increasing myocardial infarct size The major agent is isoprenaline

Secondly *when complications call for treatment* those agents should be used which are thought to reduce infarct size everything else being equal For example if load reduction be required in the presence of left ventricular failure then currently available literature would suggest a role for nitrates (especially long acting oral compounds) to reduce the preload (and possibly the afterload)

Thirdly when there is clinical or laboratory evidence of reinfarction or extension of the infarction process the case for therapeutic intervention becomes stronger

Each agent has some arguments for a specific use Thus β blockade may be indicated for

Table VIII Possible harmful side effects of four anti infarct agents

	Heart failure	Hypotension	Bradycardia	Heart block	Tachycardia	Fluid and electrolyte problems
β-blockade	Yes	Yes	Yes	Yes	No	No
GIK	No	No	No	?†	No	Yes
Nitrates	No	Yes	Yes‡	No	Yes	No
Hyaluronidase	No	No	No	No	No	No

N t with intra enous nitroglycerin or oral isosorbid din trate
Rarely found in presence of LV f lure or hyperten n
Very rapid glucose and K measurements now a a l bl to avoid excess e hyperglycemia or cess deviations in blood K
†M y prolo g cond ct on time in healthy pat nts no spec fic d ta o patient with infar tion but not reported s side effects.
‡Seven case reports. ** Mech nism u known

tion[21] However the complex hemodynamic effects of oxygen in some patients[1] mean that ischemic damage would not necessarily improve

Lidocaine although given as an antiarrhythmic agent reduces epicardial ST elevation when given at a dose of 3 mg /kg in dogs with coronary occlusion[21] Lidocaine also reduces ischemic damage during cardiopulmonary bypass[22] Lidocaine decreased catecholamine induced enzyme release from the isolated perfused rat heart Lidocaine also improved myocardial blood flow by 60% in patients studied 15 days after acute myocardial infarction Thus lidocaine would probably improve ischemic damage but firm data are lacking

Verapamil is also primarily an antiarrhythmic drug used for supraventricular tachycardia but decreases experimental infarct size[10] possibly by selectively decreasing the contractility of the ischemic zone[2]

Disopyramide given orally (100 mg four times daily) as soon as possible after admission to hospital has very recently been reported to limit extension of infarction to decrease serious arrhythmias and to decrease mortality rate[2,3] The design of this study can be criticized chiefly because the control mortality rate was so high These observations therefore need confirmation but do suggest the feasibility of more effective therapy for patients not managed in a coronary care unit

Antiarrhythmic agents may therefore in general be held to have anti ischemic effects In addition to the effects of lidocaine verapamil and disopyramide β blockade has antiarrhythmic effects[1] as do nitrates Glucose insulin potassium is antiarrhythmic in dog infarcts[1] The mechanisms linking infarct size and arrhythmias are ill understood but it is reasonable to conclude that the use of antiarrhythmic agents will in general reduce infarct size and the use of anti infarct agents will in general reduce arrhythmias because patients with large infarcts also tend to have more arrhythmias[1]

Digitalis as acetyl strophanthidin when given to patients without overt heart failure 11 to 19 hours after the onset of symptoms could greatly increase infarct size as estimated by creatine kinase release curves[31] However animal data suggest that digitalis compounds when given in the presence of cardiomegaly could exert a beneficial effect on infarct development probably by reduction of heart size and myocardial oxygen demand[5] In the presence of uncontrolled atrial fibrillation digitalis compounds could also be expected beneficially to influence infarct size by reducing the heart rate Finally digitalis compounds can limit the depressant effects of β blockade on the ischemic dog myocardium and thereby actually decrease ischemic injury[76]

Diuretics should act to reduce infarct size in the presence of left sided failure by reducing the preload and hence the heart size

Aminophylline may be used in the presence of bronchospasm associated with left ventricular failure However by inhibition of phosphodiesterase it may increase cardiac cyclic AMP also with an arrhythmogenic effect[2] In critically ill patients there was an inordinately high incidence of cardiac arrest which followed intravenous administration of aminophylline[7,8] Aminophylline is thus probably too suspect to allow its evaluation in relation to infarct size

Morphine has not been studied for effects on infarct size There is some evidence that its effect in pulmonary edema is antiadrenergic[79] in addi

requirement for hemodynamic or metabolic intervention in any given patient could be better assessed

The strongest evidence for the use of anti infarct agents stems from experience with β blockade but even there there is as yet no evidence that reduction of ischemic injury and enzyme release leads to improved long term prognosis

The short history of the therapeutic approach to myocardial infarction has already seen anticoagulants and hypocholesterolemic agents running into strong counterarguments Thus it is prudent to emphasize three major problems

First the hypothesis that a large infarct size is associated with more complications and a higher mortality rate seems acceptable in the light of present evidence [2 34] however the converse hypothesis (therapeutically induced decrease of infarct size fewer complications and lower mortality rate as a result of therapy) still requires proof even though it might seem a self evident truth

Second the data on patients are scanty especially when it comes to effects on indices of infarct size as opposed to indices of ischemic injury

Third until a rapid on line method for the assessment of the development of the infarct process becomes available it will be difficult to select a therapy to meet the specific needs of an individual patient

Conclusions In spite of severe reservations about how best to measure or modify infarct size the concept of modification of infarct size has introduced an entirely new dimension into our management of acute myocardial infarction

Professor A Maseri Fisiologia Clinica Pisa and Charles E Rackley M D kindly provided manuscripts in press I thank Brian M Kennelly M D., and Bernard Gersh M D., for many useful discussions This manuscript forms part of the research program supported in part by the Medical Research Council of South Africa and by the Chris Barnard Fund

Addendum

Since this article was prepared in 1978 two preliminary reports have shown a relation between the use of anti infarct agents and a reduction in mortality in acute myocardial infarction An infusion of nitroprusside for 24 hours followed by isosorbide dinitrate for 7 days reduced death and ventricular fibrillation GIK improved mortality in the randomized trial provided that patients with a low cardiac index or a high pulmonary artery end diastolic pressure were excluded Because both nitrates and GIK appear to have antiarrhythmic properties these studies do not prove a protective effect of limitation of infarct size per se Another study suggests that spasm is not the usual initial event in acute myocardial infarction [261] thereby arguing against relief of spasm as a mode of action of nitrates in acute infarction

REFERENCES

130 Kloner R A Fishbein M C Lew H Maroko P R and Braunwald E Mummification of the infarcted myocardium by high dose corticosteroid Circulation 57 56 1978

131 Shanks, R G The properties of beta adrenoceptor antagonists Postgrad Med J 52 14 19 6

132 Srivastava S C Dewar H A and Newell, D J Double blind trial of propranolol (Inderal) in angina of effort Br Med J 2 724 1964

133 Reimer K A Rasmussen M M and Jennings R B Reduction by propranolol of myocardial necrosis following temporary coronary artery occlusion in dogs Circ Res 33 353 1973

134 Rasmussen M M Reimer K A Kloner R A, and Jennings R B Infarct size reduction by propranolol before and after coronary ligation in dogs Circulation 56 794 1977

135 Opie L H and Thomas M Propranolol and experimental myocardial infarction substrate effects Postgrad Med J 52 124 1976

136 Peter T Heng M K Singh B N Ambler P Nisbet N Elliot R and Norris R M Failure of high dose propranolol to reduce experimental ischemic damage Circulation 57 534 1978

137 Marshall R J and Parratt J R Comparative effects of propranolol and practolol in the early stages of experimental canine myocardial infarction Br J Pharmacol 57 295 1976

138 Kloner R A., Reimer K A and Jennings R B Distribution of coronary collateral flow in acute myocardial ischaemic injury effect of propranolol, Cardiovasc Res. 10 81 1976

139 Vatner S F., Baig H Manders, W T Ochs H and Pagani M Effects of propranolol on regional myocardial function electrograms and blood flow in conscious dogs with myocardial ischemia J Clin Invest 60 ... 1977

140 Mueller H S Ayres S M Religa A and Evans R G Propranolol in the treatment of acute myocardial infarction Effect on myocardial oxygenation and hemodynamics Circulation 49 10 8 19 4

140A Mueller H S and Ayres, S M Metabolic responses of the heart in acute myocardial infarction in man Am J Cardiol 42 363 1978

141 Jewitt D E., Burgess, P A and Shillingford, J P The circulatory effects of practolol (ICI 50172) in patients with acute myocardial infarction Cardiovasc Res 4 188 1970

142 Harry J D Kappagoda C T., Linden R J and Snow H M Action of propranolol on the dog heart, Cardiovasc Res 7 729 19 3

inappropriate tachycardia but proof of the efficacy of agents other than practolol is awaited In such patients with heart rates over 100 per minute practolol started within a few hours of the onset of symptoms and then continued has been shown to improve the mortality rate up to one year post infarct but prolonged therapy with practolol can no longer be accepted Some studies[145] and theoretical considerations (Part I of this review) suggest that β blockade could be given to all patients seen early enough and in whom β blockade is not contraindicated provided there is appropriate monitoring in a coronary care unit Furthermore ideal properties of the β blocker (especially in relation to intrinsic sympathetic activity) remain to be determined Whether the possible harmful effects (e g brady cardia hypotension and conduction disturbance) would outweigh the beneficial effects would depend on the success of the monitoring procedures And the possible use of oral β blocking agents other than practolol which is no longer available requires clinical trial Thus further experiments with other β blocking agents is required before definite guidelines can be formulated in such patients

GIK may be an inotropic agent which does not extend infarct size Long acting nitrates are of proven use in selected patients with left ventricular failure complicating acute myocardial infarction but the effects on infarct size are not known Hyaluronidase may come to be the most suitable nonspecific therapy for patients seen in the early hours of the development of the heart attack In every case the results of large scale randomized trials with mortality as end point are awaited and such results will affect the recommendations to be made

Of the agents considered only hyaluronidase and GIK can be given without hemodynamic monitoring in a coronary care unit and GIK requires metabolic monitoring While it would seem ethically acceptable for the agents discussed to be used in individual patients by physicians who understand the problems involved the benefit remains hidden and only the results of large scale randomized trials could uncover the real benefit there might be Until a rapid on line method of measuring an index of infarct size is available assessment of the therapeutic requirements of the individual patient will not be clearly defined

Table X Effect of repetitive intravenous injections of practolol on ST segment elevation (Based on data of Pelides et al [3])

Patient	Times of study (hr post-onset)	Late effect as % of early effect	
		% reduction ST area	% reduction ST elevation
CN	18 and 66 hrs	19%	33%
DW	14 and 38 hrs.	30%	3%
FF	27 and 72 hrs	43%	48%

In summary it must be emphasized that the subject is in the early stages of development The ideal must be to obtain more information on the use of anti infarct agents by rigorously conducted therapeutic trials It would be especially important to obtain studies on the effect of such agents on short and long term mortality rates and for this multicenter trials would be needed In the meantime there are arguments for and against each of the four agents here reviewed

10 What can be hoped for?

Thusfar we have information that two anti infarct measures afterload reduction and hyaluronidase decreased indices of infarct size and that the extent of effect was about 25% in patients judged respectively by creatine kinase curves or Q wave effects Furthermore propranolol decreased creatine kinase release by about 30% [3] Quantification in patients in other cases is not available but a variety of agents decreased measured infarct size by 40% in animals[160] The difference may well be because only patients with a collateral circulation appear to respond to β blockade[31] which could readily be explained by the requirement of a collateral circulation [3, 33] to create a zone of ischemia of lesser severity on which the anti infarct agent should be most active

If the average infarct were to be reduced by only 25% the effect on mortality rate may well not be striking although even a relatively small reduction in infarct size of every individual treated could make a substantial difference in the cumulative mortality rate of a country like the United States of America where acute myocardial infarction is common However the effect on the individual patient will generally not be striking unless new techniques are developed to allow more specific monitoring of the rate at which the infarction process unfolds so that the

ventricular vulnerability during acute myocardial ischaemia in the dog J Molec Cell Cardiol 11 31 1979
177 Wildenthal K., Mierzwiak D S and Mitchel J H Acute effects of increased serum osmolality on left ventricular performance Am J Physiol 216 898 1969
178 Sodi Pallares, D Metabolic intervention—use of GIK Circ Res (Suppl 1) 38 72, 1976
179 Opie L H Tansey M J and Kennelly B M Proposed metabolic vicious circle in patients with large myocardial infarcts and high plasma free fatty acid concentrations Lancet 2 890 1977
180 Rackley C E Russell R O Jr Rogers W J Mantle J A. McDaniel, H G and Reddy W J Myocardial metabolism in coronary artery disease *in* Coronary Artery Disease Rackley C E., and Russell R O Jr eds Mt Kisco N Y 1979 Futura Publishing Co Inc
181 Mantle J A Russell, R O Jr Rogers W J McDaniel H G and Rackley C E Metabolic support of ventricular function in patients with myocardial infarction by an infusion of glucose insulin potassium (Abstract) Clin Res 24 228 1976
182 Allison S P., Morley C J and Burns-Cox C J Insulin glucose and potassium in the treatment of congestive heart failure Br Med J 3 675 1972
183 Mittra B Potassium glucose and insulin treatment of heart block after myocardial infarction Lancet 2 1438 1966
184 Gould, L. Reddy C V and Gomprecht R F Effect of glucose insulin potassium on the human conduction system Am J Cardiol. 33 498 1974
185 Brunton T L On the use of amyl in angina pectoris Lancet 2 97 1867
186 Robinson B F Relation of heart rate and systolic blood pressure to the onset of pain in angina pectoris Circulation 35 1073 1967
187 Robin E Cowan C Puri P Ganguly S De Boyne E., Martinez, M Stock T., and Bing R J A comparative study of nitroglycerin and propranolol Circulation 36 175 1976
188 Becker L C Fortuin N J and Pitt B Effect of ischemia and antianginal drugs on the distribution of radioactive microspheres in the canine left ventricle Circ Res. 28 263 1971
189 Bache R J Effect of nitroglycerin and arterial hypertension on myocardial blood flow following acute coronary artery occlusion in the dog Circulation 57 557 1978
190 Epstein S E Kent K M Goldstein R E., Borer J S and Redwood D R Reduction of ischemic injury by nitroglycerin during acute myocardial infarction N Engl J Med 292 29 1975
191 Delgado C E Pitt B., Taylor D R Weisfeldt M L., and Kelly D T Role of sublingual nitroglycerin in patients with acute myocardial infarction Br Heart J 37 392, 1975
192. Borer J S Redwood D R., Levitt B., Cagin N Bianchi C Vallin H and Epstein S E Reduction in myocardial ischemia with nitroglycerin nitroglycerin plus phenylephrine administered during acute myocardial infarction N Engl. J Med. 293 1008 1975
192A. Bussmann W D and Schupp D Effect of sublingual nitroglycerin in emergency treatment of severe pulmonary edema Am J Cardiol 41 931 1978
192B Armstrong P W Walker D C Burton J R and Parker J O Vasodilator therapy in acute myocardial infarction A comparison of sodium nitroprusside and nitroglycerin Circulation 52 1118 1975.
193 Come P C Flaherty J T Baird, M G Rouleau J R Weisfeldt M L. Green H L., Becker L. and Pitt B Reversal by phenylephrine of the beneficial effects of intravenous nitroglycerin in patients with acute myocardial infarction N Engl. J Med. 293
1975
194 Flaherty J T Reid P R Kelly D T Taylor D R Weisfeldt M L. and Pitt B Intravenous nitroglycerin in acute myocardial infarction, Circulation 51
1975
195 Flaherty J T Come P C Baird M G Rouleau J Taylor D R Weisfeldt M L., Greene H L., Becker L C and Pitt B Effects of intravenous nitroglycerin on left ventricular function and ST segment changes in acute myocardial infarction, Br Heart J 38
1976
196 Derrida J P Sal R., and Chiche P Nitroglycerin infusion in acute myocardial infarction (Letter) N Engl J Med 297 336 1977
197 Bussman W D Lochner J and Kaltenbach, M Orally administered isosorbide dinitrate in patients with and without left ventricular failure due to acute myocardial infarction Am J Cardiol 39 91 1977
198 Perret C Gardaz J P Reynaert, M Grimbert, F and Enrico J F Phentolamine for vasodilator therapy in left ventricular failure complicating acute myocardial infarction Haemodynamic study Br Heart J 37
1975
199 Franciosa J A Guiha N H Limes, C J Rodriguez E and Cohn J N Improved left ventricular function during nitroprusside infusion in acute myocardial infarction Lancet 1 650 1972
200 Chiarello M Gold H K Leinbach R. C Davis M A and Maroko P Comparison between the effects of nitroprusside and nitroglycerin on ischemic injury during acute myocardial infarction Circulation 54
1976
201 Kotter V Von Leitner E R. Wunderlich, J and Schroder R Comparison of haemodynamic effects of phentolamine sodium nitroprusside and glyceryl trinitrate in acute myocardial infarction Br Heart J 39 1196 1974
202 Mann T Cohn P F Holman B L., Green, L H Markis J E and Philips, D A Effect of nitroprusside on regional myocardial blood flow in coronary artery disease Results in 25 patients and comparison with nitroglycerin Circulation 57 73 1978
203 de Oliveira J M Carballo R and Zimmerman, H A Intravenous injection of hyaluronidase in acute myocardial infarction preliminary report of clinical and experimental observations. Am Heart J 57
1959
204 de Oliveira J M and Levy M N Effect of hyaluronidase upon the water content of ischemic myocardium Am Heart J 60 106 1960
205 Most A S Capone R J and Mastrofrancesco P Failure of hyaluronidase to alter the early course of acute myocardial infarction in pigs. Am. J Cardiol 38 28 1976
206 Maroko P R Hillis L. D Muller J E., Tavazzi L Heyndrickx G R May M., Chiariello M Distante A Askenazi, J Salerno J Carpentier J Reshetnaya N I Radvany P., Libby P., Raabe D S Chazov E I., Bobba P and Braunwald E. Favorable effects of hyaluronidase on electrocardiographic evidence of necrosis in patients with acute myocardial infarction N Engl J Med 296 898 1977
207 Askenazi J., Hillis L. D Diaz, P F Davis M A

143 Pelides, L J Reid D S Thomas M., and Shillingford J P Inhibition by β blockade of the ST segment elevation after acute myocardial infarction in man Cardiovasc Res 6 295 1972
144 Newman R J Comparison of the antilipolytic effect of metoprolol, acebutolol and propranolol in man Br Med J 2 601 1977
145 Peter T Norris, R M., Clark E D Heng M K Singh B N Williams B Howell D R., and Abler P K Reduction of enzyme levels by propranolol after acute myocardial infarction Circulation 57 1091 1978
146 Barber J M Boyle D Mc C Chaturvedi, N C., Singh, N and Walsh M J Practolol in acute myocardial infarction Acta Med Scand Suppl 587 213 1976
147 Mathey D Bleifeld W Hanrath P., and Effert S Attempt to quantitate relation between cardiac function and infarct size in acute myocardial infarction Br Heart J 36 271 1974
148 Green K G and 76 other authors Improvement in prognosis of myocardial infarction by long term beta adrenoreceptor blockade using practolol Br Med J 3 735 1975
149 Wilhelmsson C Vedin J A Wilhelmsen L Tibblin G and Werko L Reduction of sudden deaths after myocardial infarction by treatment with alprenolol Lancet 2 1157 1974
150 Anonymous Beta blockade after myocardial infarction Drug Ther Bull 15 1 1977
151 Sowton E Das Gupta D S and Baker I Comparative effects of beta adrenergic blocking drugs Thorax 30 9 1975
152 Ku D D and Lucchesi B R Effects of dimethyl propranolol (UM 272 SC 27761) on myocardial ischemic injury in the canine heart after temporary coronary artery occlusion Circulation 57 541 1978
153 Mulholland H C., and Pantridge J F Heart rate changes during movement of patients with acute myocardial infarction Lancet 1 1244 1974
154 Devlin J E Mulholland H C Kelly M J H Webb S W MacKenzie G., and Adgey A. A J Control of heart rate during movement in acute myocardial infarction Eur J Cardiol. 7 147 1978
155 Opie L H and Stubbs W A Carbohydrate metabolism in cardiovascular disease Clin Endocrinol Metab 5 703 1976
156 Calva E Mujica A Bisteni, A and Sodi Pallares D Oxidative phosphorylation in cardiac infarct Effect of glucose KCl insulin solution Am J Physiol 209 371 1965
157 Sodi Pallares D., Bisteni A Medrano G A de Micheli A de Leon J Ponce Calva E Fishleder B L Testelli M R and Miller B L The polarizing treatment in cardiovascular conditions *in* Bajusz E editor Electrolytes and cardiovascular diseases II Basel 1966 S Karger pp 198 238
158 Surawicz, B Evaluation of treatment of acute myocardial infarction with potassium glucose and insulin Progr Cardiovasc Dis 10 545 1968
158A Obeid A I Verner R L and Lown B Influence of glucose insulin and potassium on vulnerability to ventricular fibrillation in the canine heart Circ Res 43 601 1978
159 Maroko P R Libby P Sobel B E Bloor C M Sybers, H D., Shell W E Covell J W and Braunwald E Effect of glucose insulin potassium infusion on myocardial infarction following experimental coronary artery occlusion Circulation 45 1160 1972
160 Maroko P R., and Braunwald E. Modifications of infarct size after coronary occlusion Ann. Intern. Med 79 720 1973
161 Opie L. H Bruyneel K., and Owen P Effects of glucose insulin and potassium infusion on tissue metabolic changes within first hour of myocardial infarction in the baboon Circulation 52 49 1975
162 Rovetto M J Whitmer J T., and Neely J R Comparison of the effects of anoxia and whole heart ischemia on carbohydrate utilization in isolated working rat hearts, Circ Res 32 699 1973
163 Heng M K., Norris, R M., Singh B N and Barratt Boyes, C The effects of glucose and glucose-insulin potassium on haemodynamics and enzyme release after acute myocardial infarction Br Heart J 39 748 1977
163A Liedtke A J., Nellis, S., and Neely J R Effects of excess free fatty acids on mechanical and metabolic function in normal and ischemic myocardium in swine Circ Res. 43 652 1978
164 Medical Research Council Potassium glucose and insulin treatment for acute myocardial infarction Lancet 2 1355 1968
165 Rogers, W J Stanley A W., Breinig J B Prather J W McDaniel, H G Moraski R E Mantle J A., Russell R O Jr., and Rackley C E Reduction of hospital mortality rate of acute myocardial infarction with glucose-insulin potassium infusion AM HEART J 92 441 1976
166 Sodi Pallares D., de Leon J Ponce Bisteni, A., and Medrano G A Potassium glucose and insulin in myocardial infarction Lancet 1 1315 1969
167 Prather J W., Russell R Mantle J., McDaniel H and Rackley C E Metabolic consequences of glucose-insulin potassium infusion in treatment of acute myocardial infarction Am J Cardiol 38 95 1976
168 Sodi Pallares, D and de Leon J Ponce Ischaemic heart disease and polarizing treatment New metabolic and thermodynamic bases, Mexico City 1976 Tampa Tracings
169 Luxton M R Miller N E and Oliver M F Antilipolytic therapy in angina pectoris reduction of exercise induced ST segment depression Br Heart J 38 1204 1976
170 Russell D C and Oliver M F Effect of antilipolytic therapy on ST segment elevation during myocardial ischaemia in man Br Heart J 40 117 1978
171 Rowe M J., Neilson J M M and Oliver M F Control of ventricular arrhythmias during myocardial infarction by antilipolytic treatment using a nicotinic acid analogue Lancet 1 295 1975
172 Russell R O., Rogers W J Mantle J A McDaniel H G and Rackley C E Glucose insulin potassium free fatty acids and acute myocardial infarction in man Circulation 53 207 1976
173 Ahmed S S Lee C., Oldewurtel H A and Regan T J Sustained effect of glucose potassium insulin on myocardial performance during regional ischemia Role of free fatty acid and osmolality J Clin Invest 61 1123 1978
174 Maroko P R Libby P Bloor C M., Sobel, B E and Braunwald E Reduction by hyaluronidase of myocardial necrosis following coronary artery occlusion Circulation 46 430 1972
175 Serur J R Urschel, C W., Sonnenblick E H and La Raia P J Experimental myocardial ischemia III Protective effect of glucose on myocardial function J Molec Cell Cardiol 8 521 1976
176 Russell, D C and Oliver M F Effect of glucose on

on myocardial perfusion and ischemic injury in dogs Circ Res. 43 372, 1978

242 Maroko P R., Bernstein E F Libby P DeLaria G A., Covell, J W Ross, J and Braunwald E Effects of intra aortic balloon counterpulsation on the severity of myocardial ischemic injury following acute coronary occlusion counterpulsation and myocardial ischemic injury Circulation 45 1150 1972

243 Shatney C H MacCarter D J and Lillehei, R C Effects of infusion of dopamine and nitroprusside on size of experimental myocardial infarct Chest 73 850 1978

244 Miller R R Awan N A., and Mason D J Nitroprusside therapy in acute and chronic coronary heart disease, Am J Med 65 167 1978

245 Da Luz P Forrestsr J S., Wyatt H L Tyberg J V Chagrasulis R Parmley W W and Swan H J C Hemodynamic and metabolic effects of sodium nitroprusside on the performance and metabolism of regional ischemic myocardium Circulation 52 400 1975

246 Maroko P R Radvany P Braunwald E and Hale S L Reduction of infarct size by oxygen inhalation following acute coronary occlusion Circulation 52 360 1975

247 Madias, J E., Madias N E and Hood W B Jr Precordial ST segment mapping 2 Effects of oxygen inhalation on ischemic injury in patients with acute myocardial infarction Circulation 53 411 1976

248 de Leiris J Lubbe W F and Opie L H Effects of free fatty acid and glucose on enzyme release in experimental myocardial infarction Nature 153 746 1975

249 Regan T J Effros R M Haider B Oldewurtel H A., Ettinger P O and Ahmed S S Myocardial ischemia and cell acidosis Modification by alkali and the effects on ventricular function and cation composition Am J Cardiol 37 501 1976

250 Libby P Maroko P R Bloor C M Sobel, B E and Braunwald E Reduction of experimental myocardial infarct size by corticosteroid administration J Clin Invest 52 599 1973

251 Roberts R., de Mello V., and Sobel B E Deleterious effects of methylprednisolone in patients with myocardial infarction Circulation 53(Suppl 1) I 204 1976

252 Powell W J., DiBona, D R Flores J., and Leaf A The protective effect of hyperosmotic mannitol in myocardial ischemia and necrosis Circulation 54 603 1977

253 Fixler D E Buja L M., Wheeler J M and W... J T Influence of mannitol on maintaining ... flows and salvaging myocardium during ventric... and during prolonged coronary artery ligation, Circulation 56 340 1977

254 Hirzel H O and Kirk E S The effect of ma... following permanent coronary occlusion Circulation 56 1006 1977

255 Opie L. H Role of carnitine in fatty acid metabolism of normal and ischemic myocardium Am Heart J 97 375 1979

256 Decker R S and Wildenthal, K W Influence of methylprednisolone on ultrastructural and cytochemical changes during myocardial ischemia Am J Path 92 1 1978

257 Selwyn, A Fox K M Welman E Jonathan, A, and Shillingford, J P Electrocardiographic precordial mapping in anterior myocardial infarction The critical period for interventions as exemplified by methylprednisolone Circulation 58 892 1978

258 Heikkila J and Nieminen M S Protection of ischaemic myocardium with intravenous ... acute myocardial infarction (Abstract) Am. J Card. 45 484 1980

259 Kim Y I and Williams J F Relief of chest pain and reduction of Q wave evolution in acute myocardial infarction by large dose sublingual nitroglycerin (Abstract) Am J Cardiol. 45 483 1980

260 Bussmann W D Passek D Seidel W and Kaltenbach M Prospective randomized trial of intravenous nitroglycerin in acute myocardial infarction (Abstract) Circulation 59 and 60(Suppl. II) II 164 1979

261 Durrer J D Lie K I and van Capelle, F J Treatment of acute myocardial infarction with sodium nitroprusside during 24 hours followed by isosorbide dinitrate (Abstract) Circulation 59 and 60(Suppl II) II 165 1979

262 Rogers W J Mantle J A McDaniel H G Russell R O and Rackley C E Prospective randomized trial of glucose insulin potassium in acute myocardial infarction (Abstract) Circulation 59 and 60(Suppl II) II 165 1979

263 Gold H K and Leinbach R C Coronary obstruction ... in anterior myocardial infarction Thrombus or spasm (Abstract) Am J Cardiol 45 433 1980

Braunwald E and Maroko P The effects of hyaluronidase on coronary blood flow following coronary artery occlusion in the dog Circ. Res. 40 566 1977
208 Rovetto M J Effect of hyaluronidase and methyl prednisolone on myocardial function glucose metabolism, and coronary flow in the isolated ischemic rat heart, Circ Res 41 374 1977
209 Kloner R A Fishbein M C., Cotran R S Braunwald E., and Maroko P R The effect of propranolol on microvascular injury in acute myocardial ischemia Circulation 55 872 1977
210 MacLean D., Fishbein M C Maroko P R and Braunwald E Hyaluronidase induced reductions in myocardial infarct size Science 194 199 1976
211 Gudbjarnason S., Fenton J C., Wolf P L., and Bing R J Stimulation of reparative processes following experimental myocardial infarction Arch Intern Med 118 33 1966
212 O Brien K P Grigor R R., and Taylor P M Intravenous diazoxide in treatment of hypertension associated with recent myocardial infarction Br Med J 4 74 1975
213 Loeb S Saudye A Croke, R P., Talano J V., Klodnycky M L. and Gunnar R M Effects of pharmacologically induced hypertension on myocardial ischemia and coronary hemodynamics in patients with fixed coronary obstruction Circulation 57 41 1978
214 Fox K M Selwyn A P Welman E Jonathan A and Shillingford J P Electrocardiographic signs and creatine kinase release in patients on beta blockers suffering acute myocardial infarction (Abstract) Br Heart J 40 435 1978
215 Selwyn A P Fox K. Welman E., and Shillingford J P Natural history and evaluation of Q waves during acute myocardial infarction Br Heart J 40 383 1978
216 Saliba M J Kuzman W J and March, D G Effect of heparin in anticoagulant doses on the electrocardiogram and cardiac enzymes in patients with acute myocardial infarction Am J Cardiol 37 605 1976
217 Madias, J E., Madias, N E., and Hood W B Jr Precordial ST-segment mapping 2 Effects of oxygen inhalation on ischemic injury in patients with acute myocardial infarction, Circulation 53 411 1976
218 Thomas M Malmcrona R and Shillingford J Haemodynamic effects of oxygen in patients with acute myocardial infarction Br Heart J 27 401 1965
219 Boudoulas H., Tyrologos A and Metaxas, P Modification of acute myocardial infarction size with lidocaine in dogs (Abstract) Am J Cardiol 35 124 1975
220 Schaub R G Stewart G Strong M., Ruotolo R and Lemole G Reduction of ischemic myocardial damage in the dog by lidocaine infusion Am J Pathol. 87 399 1977
221 Gould L. Reddy C V R Hayt D B., Blatt C J and Gomprecht R. F Lignocaine Effects on coronary blood flow in patients with recent myocardial infarction, Br Heart J 36 566 1974
222 Smith H J Goldstein R A., Griffith J M Kent, K M and Epstein S E Regional contractility Selective depression of ischemic myocardium by verapamil, Circulation 54 629 19 6
223 Zainal, N., Carmichael D J S Griffiths, J W Besterman E M M Kidner P H Gillham A. D and Summers G D Oral disopyramide for the prevention of arrhythmias in patients with acute myocardial infarction admitted to open wards, Lancet 2 887 1977
224 Roberts, R Husain A Ambos, H D Oliver G C Cox, J R Jr and Sobel B E. Relation between infarct size and ventricular arrhythmias Br Heart J 37 1169 1975
225 Watanabe T., Covell J W., Maroko P R., Braunwald E and Ross J., Jr Effects of increased arterial myocardial ischemia in the acutely depressed heart Am J Cardiol 30 371 1972.
226 Vatner S F., Baig C Manders W T., and Murray P A. Effects of a cardiac glycoside in combination with propranolol on the ischemic heart of conscious dogs Circulation 57 568 1978
227 Lubbe W F., Podzuweit T., Daries, P S., and Opie L. H The role of cyclic adenosine monophosphate in adrenergic effects on ventricular vulnerability to fibrillation in the isolated perfused rat heart, J Clin. Invest. 61 1260 1978
228 Camarata S J Weil M H., Hanashiro P K., and Shubin H Cardiac arrest in the critically ill I. A study of predisposing causes in 132 patients, Circulation 44 688 1971
229 Ward J McGrath, R. L., and Weil J V Effects of morphine on the peripheral vascular response to sympathetic stimulation Am J Cardiol. 29 659 1972.
230 Todres D The role of morphine in acute myocardial infarction AM HEART J 81 566 1971
231 Shillingford, J P., and Thomas, M. Cardiovascular and pulmonary changes in patients with myocardial infarction treated in an intensive care and research unit Am. J Cardiol 20 484 1967
232 Prinzmetal M Bergman N C., Kruger N F., Schwartz, L. L Simkin B., and Sobin S S Studies on the coronary circulation III Collateral circulation of beating human and dog hearts with coronary occlusion AM HEART J 35 689 1948
233 Stephan K., Meesman W., and Sadony V Oxygen demand and collateral vessels of the heart Factors influencing the severity of myocardial ischaemia after experimental coronary artery occlusion, Cardiovasc Res. 9 640 1975
234 Waagstein F and Hjalmarson A C Double-blind study of the effect of cardioselective beta blockade on chest pain in acute myocardial infarction Acta Med Scand Suppl. 587 201 1976
235 Waagstein F and Hjalmarson A. C Effect of cardioselective beta blockade on heart function and chest pain in acute myocardial infarction Acta Med. Scand. Suppl. 587 193 19 6
236 Weintraub R M Voukydis, P C., Aroesty J M., Cohen S I Ford P Kurland, O S., La Raia P J Morkin E., and Paulin S Treatment of preinfarction angina with intra aortic balloon counterpulsation and surgery Am J Cardiol. 34 809 1974
237 Kent, K, M., Smith, E R Redwood, D R., and Epstein S E Beneficial electrophysiologic effects of nitroglycerin during acute myocardial infarction Am J Cardiol. 33 513, 1974
238 Come P C and Pitt B Nitroglycerin induced severe hypotension and bradycardia in patients with acute myocardial infarction Circulation 54 624 1976.
239 Saliba M J., Covell, J W., and Bloor C M Effects of heparin in large doses on the extent of myocardial ischemia after acute coronary occlusion in the dog Am J Cardiol. 37 599 1976
240 Moschos, C B Lahiri, K., Peter A., Jerani, M U., Regan T J and Newark N J Effect of aspirin upon experimental coronary and non-coronary thrombosis and arrhythmia AM HEART J 84 525 1972.
241 Henry P D Shuchlieb R., Borda, L. J., Roberts R., Williamson, J R and Sobel, B E Effects of nifedipine



Fig 1 The left ventricular outflow tract of a patient with hypertrophic cardiomyopathy is displayed. The anterior mitral valve leaflet has been reflected. Clinically obstruction was present. Severe endocardial thickening below the aortic valve is present together with two systolic (Zahn Schmincke) pockets

Several familial studies have established that hypertrophic cardiomyopathy is a genetically transmitted disease but sporadic occurrence is well recognized

Historical note

Attention to this condition was drawn by Brock in 1957 who illustrated in his report a case of functional obstruction of the left ventricle the patient having been diagnosed clinically as suffering from aortic valve stenosis. At operation the aortic valve was found to be normal and a subaortic muscular bulge of the interventricular septum was noted. The following year the pathology of this condition was detailed. The condition was however recognized in the nineteenth century and Dittrich in 1852 was credited with the first description of this disorder. This credit was misplaced as Dittrich's patient suffered from fibrous subvalvular stenosis. More recently Liouville in 1869 and Hallopeau in 1869 have been credited with the first descriptions of hypertrophic cardiomyopathy. As early as 190[illegible] the disease was called left sided muscular con[illegible] stenosis and a disturbance of embryonic gr[illegible] was suggested as the possible etiologic mecha[illegible]nism

Since the description in 195[illegible] innumerable reports on this condition have appeared in the literature. Great diversity of opinion does ex[illegible] as to whether or not the appearances are pathognomonic or characteristic or whether the changes are non specific merely reflecting severe hypertrophy

The purpose of this review is to critically analyze the various observations that have been reported by numerous workers and to eval[illegible] their findings in order to ascertain whether or not a diagnosis can be achieved pathologically. It is proposed to describe the findings under three major headings macroscopic appearances, microscopic appearances and electron microscopic changes. The description by Teare [illegible] detailed first any subsequent additional obser[illegible]

The pathology of idiopathic hypertrophic subaortic stenosis (hypertrophic cardiomyopathy) A critical review

E G J Olsen M D F R C Path
London England

Idiopathic hypertrophic subaortic stenosis (IHSS) or hypertrophic cardiomyopathy belongs to the group of diseases designated cardiomyopathy a term introduced by Brigden in 1957 Older classifications separated primary forms (where the cause of the heart muscle disease was unknown) and secondary forms (where a disease process elsewhere in the body was associated with cardiovascular manifestations) Much confusion about the classification has arisen since that time and it was suggested that cardiomyopathy should be restricted to those entities in which the cause was unknown (the previous primary group) and that secondary cardiomyopathy should be replaced by the term specific heart muscle disease

Not only has confusion reigned regarding classification but the various types of cardiomyopathy masquerade under several synonyms which for IHSS or hypertrophic cardiomyopathy include functional obstruction of the left ventricle[3] asymmetrical hypertrophy of the heart pseudo aortic stenosis produced by ventricular hypertrophy[5] familial muscular subaortic stenosis obstructive cardiomyopathy simulating aortic stenosis idiopathic hypertrophic subaortic stenosis muscular subaortic stenosis functional subaortic stenosis diffuse subvalvular aortic stenosis[1] muscular subvalvar aortic stenosis hereditary cardiovascular dysplasia hypertrophic subvalvular aortic stenosis[4] subvalvular aortic stenosis of muscular type[5] idiopathic cardiac hypertrophy simulating valvular heart disease[16] hypertrophic obstructive cardiomyopathy[17] primary idiopathic myocardial obstructive hypertrophy[5] hypertrophic cardiomyopathy[9] and hypertrophic cardiomyopathy with or without obstruction[20, 21] Of these many synonyms the terms idiopathic hypertrophic subaortic stenosis and hypertrophic cardiomyopathy have emerged as those most frequently used throughout the world

Despite many suggestions of a possible etiology (or etiologies) no cause for hypertrophic cardiomyopathy has so far been firmly established and therefore this entity belongs by definition to this group of cardiac diseases

The incidence of IHSS is difficult to ascertain in view of the reports having been published from specialized centers Judging from comparative surveys and personal experience it appears that hypertrophic cardiomyopathy occupies an intermediate position in incidence between the other two types of cardiomyopathy the dilated (congestive) type on the one hand and the restrictive/obliterative type which is the rarest form on the other

The earlier British nomenclature (hypertrophic obstructive cardiomyopathy) implied that the obstruction was an essential element of the clinical manifestations Increased clinical experience has however shown that the obstruction is incidental[9] and that the essential hemodynamic abnormality is failure of diastolic compliance

The disease may affect any age varying from the newborn to old age the oldest patient reported being 87 years old[2]

Males are more commonly affected than females in some series[7, 8] but an equal sex incidence has been noted by others[1] In most series the disease is diagnosed in early adult life

From the N ti n l He rt Hospital Lond Engla d
Recei d f r publ c tion Sept 17 1979
Reprint requests Dr E G J Olsen Natio al He t Hosp tal Westmorel nd Street Lond n W1M 8BA Engla d

000? 8 03/80/100553 + 10$01 00 0 © 1980 The C V Mosby Co

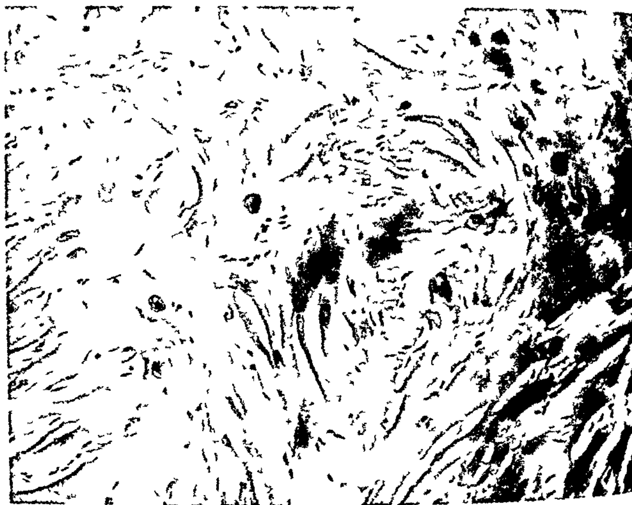


Fig 2 H t r raph f the myocardium from the septal region from a patient firmly diagnosed clinically as affec n h pe phic ardiomyopathy Extensive disarray of myocardial fibers and attempts at whorl m present In addition severe hypertrophy and an increase in collagen tissue interrupting muscle h ll seen Nuclear changes are not prominent Perinuclear halos are absent Although not all diagnostic m e n this illustration the combination of the changes present characterizes this condition H n at lin l eosin stain original magnification ×650)

with congenital heart disease is unreliable This applied particularly to the situation when marked absolute thickening was absent In a clinical and echocardiographic follow up study over a period of two years it has also been shown that resolution of the septal thickening may occur Asymmetric septal thickening can occur in normal embryonic and fetal hearts as well as in the newborn Its association with right ventricular congenital anomalies was stressed Rarely did it accompany abnormalities of left heart development It was therefore suggested that significant asymmetric hypertrophy in the adult heart and in the proper clinical setting can be a valuable diagnostic clue to the presence of hypertrophic cardiomyopathy

Analyzing these various reports there is fairly uniform agreement that minor degrees of asymmetric septal thickening are non specific A severe degree of asymmetric septal thickening in combination with right ventricular congenital anomalies is also not a reliable feature of associated hypertrophic cardiomyopathy Also septal asymmetric hypertrophy even when associated with left sided cardiac anomalies is suggestive of cardiomyopathy In any event great caution must be exercized in interpreting this finding and confirmatory histologic evidence should always be sought

Hypertrophic cardiomyopathy has been noted to occur in a variety of other cardiovascular abnormalities such as lentigenosis congenital abnormalities Turner s syndrome hypertension arterial disease isolated dextroversion and Friedreich s ataxia Unless other evidence exists the presence of asymmetric hypertrophy of the

tions that have been made will then be detailed and each section will be summarized separately in the light of the more recent findings

Macroscopic appearances

Asymmetric hypertrophy of the interventricular septum is striking on naked eye examination and consists of a localized and diffuse hypertrophy of the interventricular septum disproportionate to the rest of the left ventricle The prominent bulge towards the mitral valve was emphasized

The asymmetric hypertrophy of the septum has been consistently confirmed [3n]

Additional descriptive features included simulation of watered silk of the interventricular septum when the ventricles had been transsected[39] Endocardial thickening of the outflow portion of the interventricular septum occasioned by the impact of the anterior mitral valve leaflet the so called mirror image of the leaflet had also been noted A heart showing endocardial thickening is illustrated in Fig 1 Abnormalities of the positioning of the anterior mitral valve leaflet have also been recorded Instead of the normal insertion of the anterior mitral valve leaflet to the base of right aortic valve leaflet in this condition insertion below the posterior aortic valve cusp was noted in two patients Thickening of the mitral valve in cases of mitral insufficiency has been observed in over half the patients In the various descriptions cavity obliteration resulting in a small ventricular cavity has been frequently noted but this is not necessarily always present[47] The normality of the coronary arteries has often been stressed

Measurements of the interventricular septum have indicated that values greater than unity are found when the ratio of the thickness of the interventricular septum and the free left ventricular wall is calculated Echocardiographic identification of asymmetric septal hypertrophy has also been undertaken[1] and a ratio of ventricular septum to posterior left ventricular free wall was 1 03 in normal individuals in patients with fixed left ventricular obstruction and in patients suffering from miscellaneous cardiovascular diseases By contrast in patients with hypertrophic cardiomyopathy the ratio exceeded 1 3 in every case

Asymmetric hypertrophy of the interventricular septum at macroscopic level was therefore considered pathognomonic of hypertrophic cardiomyopathy More recently doubt has been cast on the reliability of this finding when observed alone or in combination with other anomalies of the heart Thus asymmetric septal thickening has been found in normal developing hearts and in association with congenital heart disease and other cardiac conditions[49, 53] In a study of eight cases with asymmetric hypertrophy further histologic examination has shown characteristic features of hypertrophic cardiomyopathy in only two of the eight cases Because of these findings and as a result of another study[50] it was concluded that disproportionate ventricular septal thickening in association with other cardiac diseases may be due to secondary hypertrophy and may not represent genetically transmitted asymmetric hypertrophy

In a study of 125 infants two years of age less interventricular septal to left ventricu free wall thickness ratios of [illegible] or more found in 25% of cases Using ric h trophy as the sole criterion for ing ciated hypertrophic cardiomy m

Table 1 Histochemical investigations

Substance
Glycogen
Neutral fat
Lipofuscin
Dehydrogenases
Reduced nicotinamide adenine dinucleotide dehydrogenase (NADH D)
Reduced nicotinamide adenine dinucleotide phosphate dehydrogenase (NADPH D)
Succinate dehydrogenase
Lactate dehydrogenase
Isocitrate dehydrogenase
β hydroxybutyrate dehydrogenase
Oxidases
Monoamine oxidase
Cytochrome oxidase
DOPA-oxidase
Lysosomal and other hydrolases
Non pecific esterase
indoxyl
α naphthyl
Acid phosphatase
Cholinesterase
Alkaline phosphatase
Adenosine triphosphatase
Phosphorylase
Leucine aminopeptidase

Methods w re carried out routi ely the others occasionally

3 Fibrosis

4 Degenerating muscle with disappearing myofibrils

5 Disorganized whorling muscle

In a longitudinal section the maximum points that could be obtained were 15 This was expressed as 100%

The material had been obtained at surgery where removal of muscle formed part of the operative procedure Comparison with tissue from similar sites also obtained by surgery from patients suffering from tetralogy of Fallot subaortic stenosis ventricular septal defects and mitral valve disease as well as patients with congestive cardiomyopathy was undertaken At the histologic level in just over one half of the patients with hypertrophic cardiomyopathy an index of over 65% was obtained permitting a diagnosis of that condition In the remaining patients overlap between those clinically diagnosed as suffering from hypertrophic cardiomyopathy and the tissue used for comparison existed

Extensive additional *histochemical investigation* had also been undertaken which is summarized in Table I Of the large number of enzymes investigated that of glycogen particularly pooling in the perinuclear areas was helpful in distinguishing hypertrophic cardiomyopathy from hypertrophy of the myocardium due to other causes This finding increased the diagnostic reliability considerably

The morphologic characteristics have not only been confirmed by most workers cited but also by others[44,7]

The specificity of disarray has however been questioned Disarray is found in hearts at the junction of the interventricular septum with the ventricular free walls in congenital heart disease including semilunar valve atresia with intact ventricular septae and tetralogy of Fallot It has also been observed in acquired heart conditions such as systemic hypertension and coronary artery disease Some disarray was also noted in normal hearts but not in the myocardium of developing embryos and fetuses despite disproportionate septal thick[illegible] Irregular arrangement of myocardial fibe[illegible] was also not marked in left ventricular inv[illegible] Therefore neither interventricular se[illegible] [illegible]pertrophy alone nor fiber disarray alo[illegible] the combination of both these features in th[illegible] [illegible] could be considered pathognomon[illegible] [illegible]rtrophic cardiomyopathy[53] In the study of patients with con[illegible] heart disease systemic hypertension cor[illegible] heart disease and patients with cor pulmonal[illegible] disarray of myocardial fibers to a mild degree [illegible] noted in all cases The extent of fiber disar[illegible] individual hearts varied considerably but [illegible] involved less than 11% of the myocardium [illegible] never more than 20% Comparison with a [illegible] with hypertrophic cardiomyopathy showed more than 50% of the myocardium was invol[illegible] not only in the septum but also in the [illegible] walls

A quantitative analysis of disorganized car[illegible] muscle cells in the ventricular septum has [illegible] recently been undertaken[71] In hypertrophic [illegible]diomyopathy septal disorganization was fou[illegible] necropsy in 94% of the 54 patients studied Di[illegible]ganization was extensive in most of th[illegible] patients involving at least five % or more in [illegible] of the sections examined and 25% or more of [illegible] sections in 56% of cases Septal disorganization [illegible] a limited extent was present in only 26% of [illegible] control patients (patients with other heart di[illegible]eases or with normal hearts) In only se[illegible] percent did the abnormally arranged myocard[illegible] fibers occupy five % or more of the tissue sect[illegible] This study has shown that widespread vent[illegible]lar septal disorganization of myocardial fi[illegible] though not pathognomonic of hypertrophied ca[illegible]diomyopathy is a very sensitive and a spec[illegible] histologic marker for this disease

Analyzing the various observations that ha[illegible] been made at the histologic level there is a[illegible] evidence that individual histologic changes ca[illegible] consistently found in hypertrophy other th[illegible] that of hypertrophic cardiomyopathy (see [illegible] example Figs 3c and 4b of reference 53) De[illegible] the unequestionable disarray these ch[illegible] should not in my opinion be interpre[illegible] as representing hypertrophic cardiomyopathy [illegible] Apart from disarray other accompany[illegible] changes such as extreme hypertrophy of fibe[illegible] bizarre nuclei perinuclear halos and increased [illegible] collagen tissue are essential for verification of th[illegible] diagnosis particularly when widely distrib[illegible] the tissue sections The presence of pools of glycogen increases the diagnostic reliability

Electron microscopic changes

Disarray of myocardial fibrils coursing [illegible] verse directions were noted at this level of inv[illegible]tigation[43] (Fig 3) In addition fibrillar degen[illegible]



Fig 3 Electron micrograph showing disarray of myocardial fibrils and widening of Z bands. (Lead citrate and uranyl acetate original magnification ×38 400)

septum cannot be used as a firm diagnostic parameter in these associated conditions

Microscopic appearances

Bizarre arrangement of bundles of myocardial fibers running in diverse directions and separated by connective tissue and clefts were noted The connective tissue was found to interrupt the muscle bundles The thickness of myocardial fibers varied and the clefts were lined by endothelial cells and covered by sparse elastic tissue resembling normal endocardium In some cases these clefts communicated with the cavity of both ventricles but as they pursued a muscle bound course functional shift of blood from one ventricle to the other was considered unlikely

In the original description thickening of the mitral valve was not emphasized Subsequently non specific thickening due to superimposition of collagen tissue on atrial surfaces of the mitral valve leaflets due to mitral insufficiency was observed in approximately half the patients [9]

Disarray of myocardial fibers has been confirmed [1, 21, 38] and was considered to be the most characteristic feature Severe hypertrophy with individual myocardial fibers measuring up to 100 microns in diameter has been observed The presence of clefts has also been reconfirmed not only in the myocardium [4] but also in the conducting system [3] Their significance is not fully understood as they have not been consistently found Their non specificity was emphasized [5, 6]

Other additional fiber alterations have been noted which consist of degenerating myocardial fibrils and the appearance of perinuclear halos as well as a whorled arrangement of myocardial fibers[6] (Fig 2) Changes in the intramural arterioles and small arteries showing medial thickening and cellular intimal proliferation have also been observed [3, 66, 6] These changes were usually mild not resulting in narrowing of the lumen of more than 50% [6]

In an attempt to quantify various histologic parameters an index (the histologic HOCM index) was devised Points from zero to three for each of the following changes were evaluated

1 Short runs of fibers interrupted by connective tissue

2 Large bizarre nuclei

changes is equally reliable If biopsy material permits only one method of analysis that of histology is preferable to ultrastructural or histochemical evaluation It should be remembered that any individual histologic feature is unreliable It is the *combination* of changes that characterize and may indeed be considered pathognomonic of hypertrophic cardiomyopathy

This review has concentrated on the morphologic aspects but it is clear that examination cannot and should not be undertaken without full knowledge of the clinical details Despite the extensive work that has been detailed in this communication there is still further need to define even more precicely the morphologic characterization as well as the clinico pathologic correlation of hypertrophic cardiomyopathy If all these factors are combined the problem as to whether an individual patient does or does not suffer from hypertrophic cardiomyopathy can then be fully solved

REFERENCES

1 Brigden W Uncommon myocardial diseases The non coronary cardiomyopathies Lancet ii 1179 1243 1957
2 Goodwin J F Primary myocardial disease Spectrum of cardiomyopathy and current classification *in* Proceedings of the Fifth Asian Pacific Congress of Cardiology Singapore Med J 14 358 1973
3 Brock R C Functional obstruction of the left ventricle (Acquired aortic sub valvular stenosis) Guys Hosp Rep 106 221 1957
4 Teare D Asymmetrical hypertrophy of the heart in young adults Br Heart J 20 1 1958
5 Bercu B A Diettert G A Danforth W H Fund E E and Ahlvin R C Pseudoaortic stenosis produced by ventricular hypertrophy Am J Med 25 814 1958
6 Brent L B Aburam A Fischer D L Moran T J Myers J D and Taylor W J Familial muscular subaortic stenosis An unrecognised form of idiopathic heart disease with clinical and autopsy observations Circulation 21 167 1960
7 Goodwin J F Hollman A Cleland W P, and Teare R D Obstructive cardiomyopathy simulating aortic stenosis Br Heart J 22 403 1960
8 Braunwald E Morrow A G Cornell W P Aygen M M and Hilbish T F Idiopathic hypertrophic subaortic stenosis Clinical hemodynamic and angiographic manifestations Am J Med 29 924 1960
9 Daoud, G Gallaher M E and Kaplan S Muscular subaortic stenosis Am J Cardiol 7 860 1961
10 Brachfeld N and Gorlin R Functional subaortic stenosis Ann Intern Med 54 1 1961
11 Kirklin J W and Ellis F H Jr Surgical relief of diffuse subvalvular aortic stenosis Circulation 24 739 1961
12 Menges J H Brandenburg R D and Brown A L Jr The clinical hemodynamic and pathologic diagnosis of muscular subvalvular aortic stenosis Circulation 24 1126 1961
13 Pare J A P Fraser R G Pirozynski W J [illegible] A and Stubbington D Hereditary cardiovascular [illegible] plasia A form of familial cardiomyopathy Am J [illegible] 31 37 1961
14 Whalen R E Cohen A I Sumner R G and [illegible] tosh H D A demonstration of the dynamic nature [illegible] hypertrophic subvalvular aortic stenosis (Abs [illegible] Clin Invest 41 1411 1962
15 Hansen P F Davidsen H G and Fabricius J [illegible] vular aortic stenosis of muscular type Acta Med Sc [illegible] 171 743 1962
16 Shabetai, R and McGuire J Idiopathic cardiac [illegible] trophy simulating valvular heart disease Am Heart J 65 124 1963
17 Cohen J Effat H Goodwin J F Oakley C M, and Steiner R E Hypertrophic obstructive cardio[illegible] thy Br Heart J 26 16 1964
18 Mattingley T W The clinical concept of p[illegible] myocardial disease A classification and a few notes on management and prognosis, Circulation 32 [illegible] 1965
19 Goodwin J F Congestive and hypertrophic cardiom[illegible] opathies A decade of study Lancet I 731 1970
20 Olsen E G J Morbid anatomy and histology in hypertrophic obstructive cardiomyopathy *in* Hyper[illegible] phic Obstructive Cardiomyopathy ed G E W Wolstenholme and M O Connor London 1971 Ciba Foundation Study Group No 37 J & A Churchill p 183
21 Goodwin J F and Oakley C M The cardiomyopathies (Editorial) Br Heart J 34 545 19 2
22 Olsen E G J Cardiomyopathies, *in* The Pathology of the Heart New York 1973 Intercontinental Book Corporation p 171
23 Beck W Cardiomyopathies in South Africa [illegible] survey of the problem and current therapeutic approaches Postgrad Med J 54 469 19 8
24 Oakley C M Clinical definitions and classifications of cardiomyopathies Postgrad Med J 48 [illegible] 1972
25 Neufeld H N Ongley P A and Edwards J E Combined con[illegible]enital subaortic stenosis and infundibular pulmonary stenosis Br Heart J 22 686 1960
26 Pomerance A and Davies M J Pathological fea[illegible] of hypertrophic obstructive cardiomyopathy (HOCM [illegible] the elderly Br Heart J 37 305 19 5
27 Braunwald E Lambrew C T Rockoff S D Ross J Jr and Morrow A G Idiopathic hypertrophic subaor[illegible] tic stenosis I *A description of the disease based on* analysis of 64 cases Circulation 30 (Suppl 4) 3 [illegible]
28 Davies M J Pomerance A and Teare R D Pa[illegible] logical features of hypertrophic obstructive cardiomyop[illegible] athy J Clin Pathol 27 529 19 4
29 Harley A and Organ E S Hypertrophic cardiomyop[illegible] athy with unusual features in a family Br Hea[illegible] 33 [illegible]5 1971
30 Emanuel R Withers R and O Brien K Do[illegible] and recessive modes of inheritance in idiopathic ca[illegible] myopathy Lancet 2 1065 19 1
31 Henry W L Clark C F and Epstein S E A[illegible] tric septal hypertrophy (ASH) The unifying link in [illegible] IHSS disease spectrum Observation regarding its pa[illegible] genesis pathophysiology and course Circulation 47 [illegible] 1973
32 Frank S and Braunwald E Idiopathic hyper[illegible] subaortic stenosis Clinical analysis of 126 patients [illegible] emphasis on the natural history Circulation 37 [illegible] 1968
33 Hudson R E B Cardiovascular Pathology Lond[illegible] 1970 Edward Arnold Publishers Ltd p [illegible]
34 Wigle F D and Silver M D Myocardial fiber d[illegible]

tion focal mitochondrial accumulation (the so called mitochondriosis) varying degrees of mito chondrial damage and increased number of lyso somes and lipofuchsin granules together with swelling of the sarcotubular system were noted Comparison with tissue obtained from cases with other conditions resulting in hypertrophy was also made Analysis of seven electron microscop ic features showed that extensive overlap between those patients with hypertrophic cardiomyopa thy and the control cases existed

By contrast other workers considered disar ray of myocardial fibrils which did not occur necessarily in all cells together with abnormally arranged myofilaments abnormal intercellular junctions and abnormalities of Z bands as con stituting distinctive changes Minor abnormali ties of myofibrillar disorganization were however noted in three out of 31 patients with congestive cardiomyopathy [73] Disorganization of myofibrils and other abnormal features have been widely confirmed [74-77]

Overlap between hypertrophic cardiomyopathy and other conditions resulting in hypertrophy of the myocardium[6] has been confirmed by oth ers [4, 8, 79] Indeed it has been suggested that intracellular disarray was more frequent in acquired heart disease than in hypertrophic car diomyopathy Irregular arranged myocardial fibrils have also been observed in the zones adja cent to experimental myocardial infarction[5, 8] and in embryonic heart muscle [8]

Analyzing the reports on electron microscopic findings *it has become clear that the features of* hypertrophic cardiomyopathy can be extensively mimicked by other cardiac conditions which result in hypertrophy If however intra and interfibrillar disarray is extensive the changes are suggestive but not pathognomonic of hypertro phic cardiomyopathy

So far distinction between two clinical groups recognized for several years has not been made In one group obstruction of the outflow of blood from the left ventricle (or right or both ventricles) played a significant role in the clinical symptoma tology In the other group of patients obstruction has never been clinically manifest Macroscopic studies have shown non uniform distribution of free wall thickening but a normal posterobasal region in non obstructive cases whereas in patients with obstruction uniform thickening of the entire left ventricular free wall was found including the posterobasal part [31, 83] Asymmetric hypertrophy of the ventricular septum was more pronounced in that group In another study absence of asymmetric hypertrophy of the inter ventricular septum was considered indicative of non obstruction during life In those cases where asymmetry of the interventricular septum was present obstruction or non obstruction may have existed [8] Absence of asymmetric hypertrophy of the septum did not deny a diagnosis of hypertro-phic cardiomyopathy [78] and dilatation of the ven tricular cavities prior to death may occur [9]

Histologic histochemical and ultrastructural changes are similar to those that have already been noted but the distribution of abnormal myocardial fibers is different in the two clinical groups In hypertrophic cardiomyopathy with obstruction the abnormal myocardial fibers and fibrils are mostly confined to the asymmetrically hypertrophied interventricular septum In cases without obstruction the fibers are distributed focally through left and or right ventricular walls including the septum [70, 84-86] These differences of distribution have been considered to account for the differences in clinical manifestations Caution of interpreting these findings was however sounded Such caution was well placed because other morphologic studies have shown wide spread involvement of left ventricular walls in cases of patients with obstruction [35] Two children with clinical evidence of obstruction have recent ly been described who showed at postmortem the characteristic distribution of non obstruc tion [87]

These studies on the different distribution of abnormal fibers and fibrils in the obstructive and non obstructive groups have shown that morpho logic criteria are not altogether reliable in relation to clinical findings The cases so far reported are relatively few and therefore further work must be undertaken to evaluate more fully these differ ences

It may finally be concluded that despite the various observations and sometimes contradicto ry interpretations of the morphologic findings at macroscopic microscopic and ultrastructural level one clear pattern has emerged When suffi cient material is available suitable for histologic histochemical and ultrastructural examination the combination of these methods permits diag nosis with a high degree of accuracy Examina tion at necropsy of macroscopic and histologic

subaortic stenosis. A study of operatively excised left ventricular outflow tract muscle in 14 patients Circulation 45 769 1972

74 Meesen H., and Poche R Beitrage zur pathologischen Anatomie der Fallotschen Fehler und zur idiopathischen Herzhypertrophie Anglo-German Med Rev 4 73 1967

75 McAllister B D., and Brown, A. L. A fine structure study of idiopathic hypertrophic subaortic stenosis. (Abstr) Am J Cardiol. 19 142 1967

76 Snijder J Dejong J., and Meister A.E F H Light microscopical, ultrastructural and histochemical aspects of hypertrophic obstructive cardiomyopathy (subaortic stenosis) J Molec Cell Cardiol. 3 81 1971

77 Ferrans, V J., Massumi, R. A., Shugoll G I., Ali N., and Roberts, W C Ultrastructural studies of myocardial biopsies in 45 patients with obstructive or congestive cardiomyopathies, *in* Recent Advances in Studies of Cardiac Structural Metabolism Vol. 2 Cardiomyopathies, Eds. Bajusz, E. and Rona, G Baltimore London Tokyo 1973 University Park Press p 231

78 Sekiguchi, M., Konno S., Hasegawa F., and Hirosawa K. Some characteristic electron microscopic pictures of diseased myocardium obtained by endomyocardial biopsy Bull. Heart Inst. Jap 14 30 1972/73

79 Dingemans, K. P., and Becker A E Specificity of cellular and myofibrillar disorientation in hypertrophic obstructive cardiomyopathy Arch. Pathol. Lab Med. 101 493 1977

80 Wilken, D E., Shorey C D., and Eikens, E Ultrastructural evidence for regeneration of heart muscle cells after experimental myocardial infarction Lancet ii 21 1970

81 Dusek, J., Rona G., and Khan, D S Healing process in the marginal zone of an experimental infarct [illegible] the surviving cardiac muscle cells, Am. J Pathol [illegible] 1971

82. Masanek, F J Histogenesis of the embryonic myocardium Am. J Cardiol. 25 149 1970

83. Henry W L., Clark, C. E., Roberts, W C Morrow A G and Epstein, S E. Differences in distribution of myocardial abnormalities in patients with obstructive and nonobstructive asymmetric septal hypertrophy echocardiographic and gross anatomic findings Circulation [illegible] 1974

84 Roberts W C., and Ferrans, V J Pathologic anatomy of the cardiomyopathies. Idiopathic dilated and hypertrophic types infiltrative types and endomyocardial disease with and without eosinophilia Hum. Pathol 6 287 1975

85 Maron, B J., Ferrans, V J Henry W L, Clark, C E Redwood D R., Roberts, W C., Morrow A G, and Epstein, S E Differences in distribution of myocardial abnormalities in patients with obstructive and nonobstructive symmetric septal hypertrophy (ASH) [illegible] and electron microscopic findings, Circulation [illegible] 1974

86 Henry W L., Clark, C E., Maron, B J Ferrans, V J Roberts, W C., Morrow A. G and Epstein, S E Distribution of the cardiomyopathic process in [illegible] correlative evidence from echocardiography and myocardial ultrastructure (Abstr) Clin. Res 21 [illegible] 1973

87 Edwards, W D Zakheim R., and Mattioli L. Asymmetric septal hypertrophy in childhood. Unreliability of histologic criteria for differentiation of obstructive and nonobstructive forms, Hum Pathol. 8 [illegible] 1977

and ventricular septal hypertrophy in asymmetrical hypertrophy of the heart (Editorial) Circulation 58 398 1978

Schmincke A Ueber linkseitige muskulose Conus stenosen Dtsch Med. Wschr 33 2082 1907

Walther R J Madoff I M., and Zinner K Cardiomegaly of unknown cause occurring in a family N Engl J Med 263 1104 1960

Teare R D The pathological recognition of obstructive cardiomyopathy *in* Cardiomyopathies eds. Wolstenholme G E W and O Connor M London 1964 Ciba Foundation publication J & A Churchill p 11

Wigle D E Adelman A. G and Silver M D Pathophysiological consideration in muscular subaortic stenosis *in* Hypertrophic obstructive cardiomyopathy ed Wolstenholme G E W and O Connor M London 1971 Ciba Foundation study group No 3 J & A Churchill p 63

Olsen E G J Cardiomyopathies Cardiovasc Clin 4 240 1972

Olsen E G J Pathology of hypertrophic obstructive cardiomyopathy Recent advances in studies of cardiac structural metabolism Vol 2—Cardiomyopathies Eds Bajusz E and Rona G Baltimore London Tokyo 1973 University Park Press p 197

Roberts W C Valvular subvalvular and supravalvular aortic stenosis Morphologic features Cardiovasc Clin 5 104 1973

2 Olsen E G J Pathological recognition of cardiomyopathy Postgrad Med J 51 ??7 1975

3 Olsen E G J Primary cardiomyopathies *in* Recent Advances in Pathology ed C V Harrison and K Weinbren London 1975 Churchill Livingstone No 9 p 5

4 Olsen E G J Postmortem findings and histologic histochemical and electron microscopic findings in myocardial biopsies from 200 patients *in* Cardiomyopathy and Myocardial Biopsy eds M Kaltenbach F Loogen and E G J Olsen Heidelberg, 1978 Springer Verlag p 52

5 Olsen E G J The pathology of cardiomyopathies A critical analysis Am Heart J 98 385 1979

6 Bjork V O Hultquist G and Lodin H Subaortic stenosis produced by an abnormally placed anterior mitral leaflet J Thorac Cardiovasc Surg 41 659 1961

7 Adelman A G McLoughlin M J Marquis, Y Auger P., and Wigle E D Left ventricular cineangiographic observations in muscular subaortic stenosis Am J Cardiol 24 689 1969

8 Henry W L Clark C E and Epstein S E Asymmetric septal hypertrophy (ASH) Echocardiographic identification of the pathognomonic anatomic abnormality of IHSS Circulation 47 225 1973

9 Maron B J Edwards J E Ferrans V J Clark C E Lebowitz E A Henry W L and Epstein S E Congenital heart malformations associated with disproportionate ventricular septal thickening Circulation 52 9 6 1975

0 Maron B J Henry W L Roberts W C and Epstein S E Comparison of echocardiographic and necropsy measurements of ventricular wall thickness in patients with and without disproportionate septal thickening Circulation 55 341 1977

1 Maron B J Edwards J E Moller J H and Epstein S E Prevalence and characteristics of disproportionate ventricular septal thickening in infants with congenital heart disease Circulation 59 1 6 1979

Larter W E Allen H D Sahn D J and Goldberg S J The asymmetrically hypertrophied septum Further differentiation of its causes. Circulation 53 19 1976

53 Bulkley B H Weisfeldt M L and Hutchins G M. Asymmetric septal hypertrophy and myocardial fiber disarray Features of normal, developing and malformed hearts Circulation 56 292 1977

54 Polani P E and Moynihan E J Progressive cardiomyopathic lentiginosis Q J Med 41 205 19?

55 *Somerville J., and Bonham Carter R. E The heart in* lentigenosis Br Heart J 34 58 1972

56 Gulotta S J Hamby R I Aronson A L and Ewing K Coexistent idiopathic hypertrophic subaortic stenosis and coronary arterial disease Circulation 46 890 1972

57 Nghiem Q X Toledo J R Schreiber M H Harris L C., Lockhart L. L. and Tyson, K R T Congenital hypertrophic sub-aortic stenosis associated with a phenotype Turner s syndrome Am J Cardiol 30 683 1972

58 Symons C Richardson P J and Feizi O Hypertrophic cardiomyopathy and hyperthyroidism A report of 3 cases Thorax 29 713 1974

59 Buxton A E Morganroth J Josephson M E Perloff J K., *and Shelburne J C Isolated dextroversion of the* heart with asymmetric septal hypertrophy Am Heart J 92 785 1976

60 Smith E R Sangalang V E Heffernan L P Welch J P., and Flemington C S Hypertrophic cardiomyopathy the heart disease of Friedreich s ataxia Am Heart J 94 428 1977

61 Leading Article Cardiac involvement in Friedreich s ataxia Br Med J 1 261 1978

62 Van Noorden S Olsen E G J and Pearse A G E Hypertrophic obstructive cardiomyopathy A histological, histochemical and ultrastructural study of biopsy material Cardiovasc Res V 118 1971

63 James, T N and Marshall T K De subitaneis mortibus XII Asymmetrical hypertrophy of the heart Circulation 51 1149 1975

64 Lev M Leffler W B Langendorf R., and Pick A. Anatomic findings in a case of ventricular pre-excitation (WPW) terminating in complete atrioventricular block Circulation 34 718 1966

65 James T N and Puech P De subitaneis mortibus IX Type A Wolff Parkinson White syndrome Circulation 50 1264 1974

66 Ferris J A J The atrioventricular node in hypertrophic obstructive cardiomyopathy Beitr Pathol 148 296 1973

67 McReynolds R A and Roberts W C The intramural coronary arteries in hypertrophic cardiomyopathy (Abstr) Am J Cardiol 35 154 19 5

68 Simonsen J Voigt J and Lyngborg K Hypertrophic obstructive cardiomyopathy A review of the pathoanatomic findings and the clinical characteristics including a report of two additional cases, Acta Path Microbiol Scand 81 174 1973

69 Alexander C S and Gobel F L Diagnosis of idiopathic subaortic stenosis by right ventricular septal biopsy Am J Cardiol 34 142 1974

70 Olsen E. G J Pathologie der primaren Kardiomyopathien Munch Med Wchschr 118 735 1976.

71 Maron B J and Roberts, W C Quantitative analysis of cardiac muscle cell disorganization in the ventricular septum of patients with hypertrophic cardiomyopathy Circulation 59 689 19 9

72 van der Bel Kahan J Muscle fiber disarray in common heart disease Am J Cardiol 40 355 1977

73 Ferrans V J., Morrow A G., and Roberts W C Myocardial ultrastructure in idiopathic hypertrophic

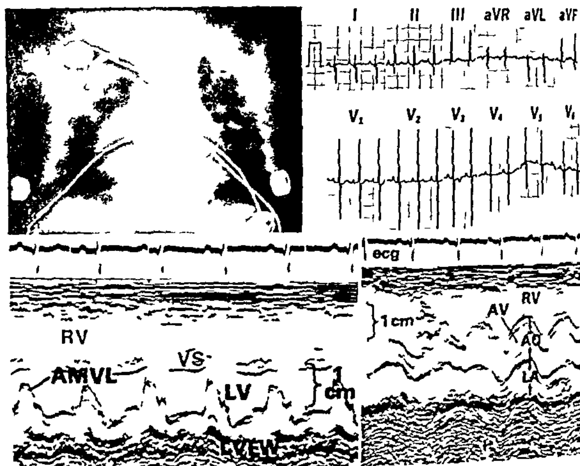


Fig 1 Posteroanterior chest radiograph *(upper left)* 2.5 months before death showing considerable prominence of the right sided chambers The pulmonary vascular markings are prominent Electrocardiogram *(ECG) (upper right)* obtained 3 months before death shows sinus tachycardia and biventricular hypertrophy The echocardiogram *(lower)* obtained 3 months before death shows the right ventricle *(RV)* left ventricle *(LV)* and left atrium *(LA)* to be of normal size The aorta *(Ao)* is at the upper limit of normal The ventricular septum (VS) moves normally *AMVL* = anterior mitral valve leaflet *AV* = aortic valve

cardiomegaly and evidences of increased pulmonary blood flow The electrocardiogram (Fig 1) disclosed biventricular hypertrophy and the echocardiogram (Fig 1) disclosed no abnormalities Despite furosemide digoxin and supplemental oxygen the congestive heart failure worsened The feeding problem was found to be the result of partial antral obstruction She died quietly

At autopsy (A79 83) the heart weighed 34 gms (expected weight for her age = 29 gms) The right atrium was clearly dilated the walls of the right atrium right ventricle and left ventricle were thickened The left atrium was normal in size The four cardiac valves were normal A large *ventricular septal defect (VSD)* located posterior and inferior to the crista supraventricularis a large ostium secundum type *atrial septal defect (ASD)* and a *patent ductus arteriosus (PDA)* were present (Fig 2)

Dr Roberts The child presented had several abnormalities associated with trisomy 13 D[...] Cabin will you describe the usual find[...] patients with trisomy 13 and contrast the[...] those in patients with trisomy 18 and 21?

Dr Cabin The abnormalities frequently f[...] in patients with trisomy 13 are listed in Ta[...] along with an indication of which abnorma[...] also are seen in trisomy 18 and 21 Our pa[...] had several of the listed abnormalities (those [...] asterisks) and consequently the diagno[...] trisomy 13 in her was obvious and also [...] confirmed by chromosome study Diagno[...] tures of trisomy 18 include small lower ja[...] palpebral fissure clenched hand short [...] narrow pelvis short stature and mental de[...] cy Characteristic findings in infants wi[...] 21 include flat facies protruded tong[...] palpebral fissures hypotonia short hand[...] mental deficiency In all three trisomy [...] congenital heart disease is common Of[...]

Clinical pathologic conference

Congenital heart disease with trisomy 13 Use of the echocardiogram in delineating the location of a left-to-right shunt

Henry S Cabin M D
Lucille A Lester M D
William C Roberts M D
Bethesda Md

DR ROBERTS Herein we will discuss a child with congenital heart disease and trisomy 13 Dr Cabin will present the patient s clinical and morphologic findings

DR CABIN J M (CC No 13 31 03) was a 4 5 month old girl who died on July 10 1979 She weighed 2 4 kilograms at birth after a 37 week gestation A precordial murmur was noted during the first 2 weeks of life and she was acyanotic At age 15 days she was transferred to the Clinical Center of the National Institutes of Health because of feeding difficulties and intermittent signs of congestive heart failure Her blood pressure was 70/40 mm Hg her heart rate was 172 beats/minute and the respiratory rate was 80 breaths/minute Her head was small (microcephaly) both eyes were small (microphthalmia) and a fissure was present in the left iris (coloboma) She had a cleft upper lip and palate a preauricular skin tag transpalmar (Simian) creases partial fusion (frog like) of her toes (syndactylism) and a rudimentary extra digit (polydactyly) on her left hand and left foot The right ventricular impulse was palpable S was single and loud and a Grade 3/6 systolic ejection type murmur was heard along the upper sternal border The lungs were clear The chest radiograph (Fig 1) disclosed

From th P th l gy B anch N tio l Heart Lung and Blood Institute and the Pediatric Met bolism B anch Natio l I stitute of Arthritis, Metabolism and Digestive Dise ses, Nation l Inst tutes of He lth, Bethesda, Md

Rece ed fo p blicat n No 1979

Reprint req ests William C Roberts, M D Chief Pathology Branch, N tional Institutes of Health N t n l He rt, Lung a d Blood Institute Bethesda Md 0014

Table I Major clinical and necropsy findings in trisomy 13 and the presence or absence of these findings in trisomy 18 and 21

	Trisomy 13	*Trisomy 18*	*Trisomy 21*
Incidence	1/5 000	1/4 000	1/700
Increased maternal age	+	+	+
Survival beyond 1 year	Rare	Rare	Rare
Male Female	1 1	1 4	1 1
Mental retardation	+	+	+
Feeding difficulty	+	+	0
Deafness	+	+	0
Congenital heart disease	+	+	+
Microcephaly	+	0	0
Microphthalmia	+	0	0
Cleft lip and palate	+	0	0
Malformed ears	+	+	+
Coloboma of the iris	+	0	0
Simian crease	+	+	+
Polydactyly	+	0	0
Syndactyly	+	+	0
Rocker bottom feet	+	+	0
Long hyperconvex fingernails	+	+	+
Undescended testes	+	+	+
Double renal pelvis	+	0	0
Absent olfactory bulbs	+	0	0
Biseptate uterus	+	0	0

I d cates that this ab rmality was present in our patient

0002-8 03/80/100563 + 04$00 40 0 1980 The C V Mosby Co

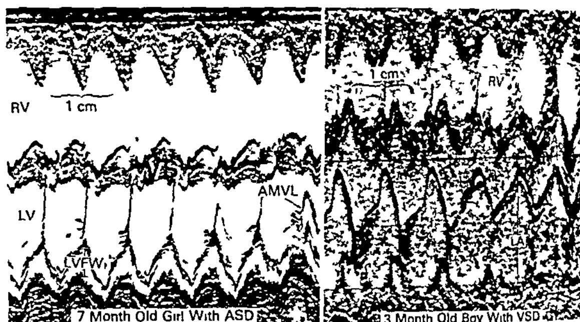


Fig 3 Echocardiograms from two patients *Left* A 7 month old girl with a secundum type atrial septal defect *(ASD)* The right ventricle *(RV)* is dilated and the ventricular septum *(VS)* moves paradoxically during ventricular systole The left ventricle *(LV)* is of normal size *LVFW* = left ventricular free wall *AMVL* = anterior mitral valve leaflet *Right* Echocardiogram from a 3 month old boy with a ventricular septal defect *(VSD)* The left atrium *(LA)* is dilated and the aorta *(Ao)* is of normal size consequently the LA to Ao ratio is increased.

cally The aorta was mildly enlarged and the left atrial to aortic ratio was normal (1 0 [normal range = 0 8 to 1 2]) These findings are of considerable help in sorting out the level of a left to right shunt Both VSD and PDA result in dilated left atria and left ventricles,[3 5] because of volume overload of the left sided chambers from the left to right shunt The right ventricle may enlarge to some extent the right atrium does not dilate An ASD causes right atrial and right ventricular volume overload without left sided enlargement This right sided overload may result in paradoxical movement of the ventricular septum during ventricular systole[6 8] Thus M mode echocardiograms in infants with VSD (Fig 3) or PDA show increased left ventricular and left atrial dimensions with increased left atrial to aortic root ratios ASD produces an increased right ventricular dimension the left ventricular and left atrial dimension are normal or smaller than normal and the left atrial to aortic root ratios are normal (Fig 3)

In our infant all three chambers seen by the M mode echocardiogram were normal in size and therefore the presence of ASD VSD or PDA as an isolated defect was most unlikely The combination however of an ASD with a PDA and/or a VSD could result in a normal sized left atrium particularly if the atrial shunt were large

The left or right ventricle could be normal or increased in size depending upon the rel[illegible] magnitude of each shunt Thus the M[illegible] echocardiogram in combination with the o[illegible] findings in our patient suggested the diagnos[illegible] ASD in combination with VSD and/or PDA

REFERENCES

1 Warkany J Passarge E and Smith L B Con[illegible] malformations in autosomal trisomy syndromes [illegible] Dis Child 112 502 1966
2 Lester L A Vitullo D Sodt P Hutcheon [illegible] Arcilla R An evaluation of the left atrial aortic r[illegible] ratio in children with ventricular septal defect Circula-tion 60 364 1979
3 Mathew R Thilenius O G and Arcilla R Com[illegible] tive response of right and left ventricles to [illegible] overload Am J Cardiol 38 [illegible] 19[illegible]6
4 Lewis A B and Takahashi M Echocard[illegible] assessment of left to-right shunt volume in children [illegible] ventricular septal defect Circulation 54 [illegible] 19[illegible]
5 Silverman N H, Lewis A B Heymann M A [illegible] Rudolph A M Echocardiographic assessment of [illegible] arteriosus shunt in premature infants Circ[illegible] 50 821 1974
6 Diamond M A Dillon J C, Haine C L, Cha[illegible] and Feigenbaum H Echocardiographic features [illegible] septal defect Circulation 43 129 19[illegible]
7 Meyer R A Schwartz D C Benzing G III [illegible] Kaplan S Ventricular septum in right ve[illegible] volume overload An echocardiographic [illegible] Cardiol 30 349 19[illegible]
8 Radtke W E Tajik A J Gau G T [illegible] T T, Giuliani E R and Tancredi R G [illegible] defect Echocardiographic observations [illegible] patients Ann Intern Med 84 [illegible] 19[illegible]

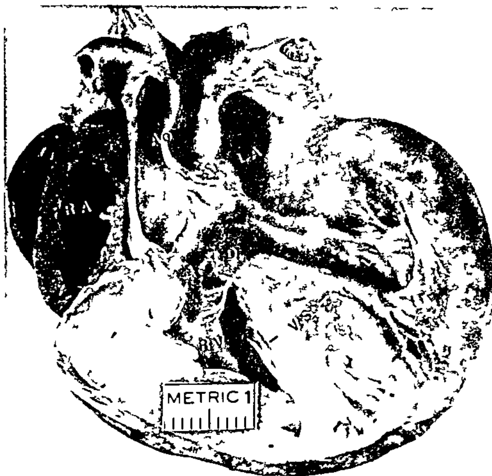


Fig 2 Longitudinal section of the heart The walls of both the right *(RV)* and left *(LV)* ventricles are hypertrophied a defect *(D)* is present in the most cephalad portion of the ventricular septum *(VS)* the right atrium *(RA)* is large and the aorta *(Ao)* and left atrium *(LA)* are of normal size (Photo by M M M Moore)

patients reported by Warkany and associates congenital heart disease occurred in 27 (84%) of 32 necropsy patients with trisomy 13 in 83 (99%) of 84 patients with trisomy 18 and in 141 (52%) of 272 patients with trisomy 21 The most commonly found malformations in trisomy 13 were VSD PDA and ASD and two or three of these three defects occurred more frequently than a single defect These three defects also were common in patients with trisomy 18 and 21 The most common type of atrial septal defect in trisomy 21 is one located in the lowermost portion of the atrial septum (ostium primum or endocardial cushion type) and in trisomy 13 and 18 the defect most commonly is in the mid portion of the atrial septum (secundum type)

The occurrence in our patient of signs of congestive heart failure acyanosis and enlarged right sided cardiac chambers with evidences of increased pulmonary blood flow strongly suggested the presence of a left to right shunt at the atrial ventricular or great artery level or combinations of these three The presence of trisomy 13 strongly suggested the presence of two or more of these defects

Dr Roberts The echocardiogram has proved useful in delineating the level of a left to right shunt Dr Lester has recently analyzed the usefulness of echocardiography for characterization and quantitation of a left to right shunt in patients with ventricular septal defect [2] Dr Lester can you summarize the echocardiographic findings in patient J M and from your previously collected data how useful is the echocardiogram in predicting the level of the shunt in patients with left to right shunts?

Dr Lester An echocardiogram was performed at 15 days of life (Fig 1) The left and right ventricles and left atrium were normal in size The ventricular septum did not move paradoxi

disease causes a granular cobblestone appearance with nodular filling defects corresponding to the exudative plaques seen endoscopically The most common viral cause of esophagitis is herpes simplex, which tends to cause focal ulcers but may produce filling defects similar to moderate monilial disease

Further investigation of the symptom of heartburn is indicated if the patient does not respond to therapy if there is a complication of the peptic esophagitis (such as stricture or ulceration) or if the diagnosis of esophagitis or gastroesophageal reflux is still in doubt Esophageal manometry demonstrates a reduced lower esophageal sphincter pressure in 80 to 100% of patients with severe reflux esophagitis[10] A normal lower esophageal sphincter pressure suggests that reflux esophagitis is not the etiology of the patient s pain In situations of continued suspicion of peptic esophagitis but equivocal manometric findings direct demonstration of acid reflux is helpful[11 1] Acid reflux may be demonstrated by placing a pH probe in the distal esophagus and instilling 0 1 N hydrochloric acid into the stomach A fall in esophageal pH below 4 suggests the presence of reflux This test has a greater than 90% yield in patients with reflux and very few false positive or false negative responses A more recent method to demonstrate reflux is the use of a radioisotopic marker ingested with an exogenous fluid load[13] Reflux of the isotope detected by gamma camera is an accurate and sensitive method but is not yet widely available

If studies have demonstrated gastroesophageal reflux but there remains a question whether the patient has esophagitis three other tests may be performed the Bernstein Test esophagoscopy and esophageal biopsy[1] The Bernstein Test is a provocative test which reproduces the classic pain of reflux esophagitis by perfusion of the esophagus with 0 1 N hydrochloric acid The acid is perfused in a blinded fashion alternating with saline Saline will relieve the discomfort by washing acid from the esophagus False positive responses are unusual and about 90 c of patients have a positive response

Esophagoscopy is helpful when it is not clear whether the patient s reflux is complicated by peptic esophagitis or when there is a complication of the peptic esophagitis such as stricture or ulceration which requires biopsy to exclude malignancy Esophagoscopy permits biopsy or cytologic examination to detect other causes of esophagitis, such as fungal or viral However the [illegible] bits of tissue obtained through the flexible [illegible] agoscope are often not adequate for [illegible] identification of reflux esophagitis Visual [illegible] ment via the esophagoscope may be falsely [illegible] tive or positive when the changes are [illegible] Biopsy of the distal esophagus by a [illegible] capsule under fluoroscopic guidance prov[illegible] accurate histologic identification of esophag[illegible] Less than 10% of normal controls will [illegible] evidence of esophagitis on such a biopsy where[illegible] approximately 90% of patients will have typ[illegible] features

Odynophagia or pain on swallowing [illegible] ond common cause of chest pain caused [illegible] esophageal disease Depending upon the und[illegible] lying etiology of the odynophagia this sym[illegible] may be precipitated by swallowing solids or [illegible] uids When the pain is the result of a m[illegible] disorder of the esophagus both solids and liqu[illegible] especially if very hot or very cold may [illegible] symptoms With obstructive lesions of the [illegible] phagus such as carcinoma or stricture od[illegible] phagia is brought on more commonly by swall[illegible] ing solid food Irritant liquids such as fruit ju[illegible] coffee or spicy drinks may cause odynophagia [illegible] there is esophagitis[18] A barium swallow is th[illegible] most important test to perform in a patient [illegible] odynophagia This test will usually demonstra[illegible] structural abnormalities such as carcinomas [illegible] strictures and occasionally the mucosal irre[illegible] larities of esophagitis or moniliasis or a m[illegible] disorder Although chest pain is a major c[illegible] plaint in only 25% of patients with achalasia [illegible] barium swallow will be abnormal in all T[illegible] characteristic findings are smooth tapering of th[illegible] distal esophagus and nonperistaltic tertiary c[illegible] tractions Diffuse esophageal spasm howev[illegible] may not show abnormalities on conventi[illegible] barium swallow in spite of chest pain

Cine radiography improves the diagnostic [illegible] curacy of the barium study when a motor d[illegible] der is present Abnormalities in mucosa produ[illegible] odynophagia will be recognized with a vari[illegible] success on barium swallow[1] If the study [illegible] good quality especially with air contrast [illegible] ing carcinomas will be easily detected The p[illegible] bility however of missing an early carcino[illegible] the esophagus as well as difficulty in de[illegible] peptic or infectious esophagiti[illegible] make [illegible] scopy an important diagnostic tool in the [illegible] tion of odynophagia

If the barium swallow suggests a motor d[illegible]

The digestive tract as a cause of chest pain

William B Long M D
Sidney Cohen M D
Philadelphia Pa

Disease of the digestive tract may cause chest pain and be the chief complaint in a patient presenting to a cardiologist A relationship of symptoms to the digestive functions of eating or defecation suggests gastrointestinal etiology The autonomic nerve supply of the esophagus is similar to that of the heart and pain from this organ often closely mimics cardiac pain Of patients referred for gastrointestinal investigation because of angina like pain but no other evidence of coronary artery disease about half are found to have an esophageal etiology for the pain Disorders of the stomach duodenum and biliary tree and less commonly colonic pancreatic hepatic or peritoneal disease can cause upper abdominal or chest pain The problem may be either a functional motility disorder or a structural pathologic entity The diagnositc problem is compounded when digestive disease and cardiac disease coexist Occasionally provocative tests designed to elicit pain from the digestive tract give assistance but frequently one must rely upon a clinical distinction

Chest pain of esophageal origin

The three major types of chest pain of esophageal origin are heartburn odynophagia (pain on swallowing) and spontaneous esophageal spasm Heartburn is characterized by retrosternal burning sensation which travels up from the xyphoid and is made worse by certain foods and by recumbency[3] In about 40% of patients pain radiates to the back and in 5% it radiates to the arms or neck[1] Heartburn is seen in increased frequency in patients with scleroderma following resection of the lower esophageal sphincter during pregnancy and during medication with certain drugs especially anticholinergics When heartburn is severe enough to be a major complaint the patient should have a barium swallow which will reveal the major complications of gastroesophageal reflux stricture and peptic ulcer of the esophagus Barium swallow demonstrates gastroesophageal reflux in 10 to 25% of patients[5] The finding of reflux may be increased to about 50% by the use of cine esophagography The water siphon test (in which a water swallow relaxes the lower esophageal sphincter) or an acid barium swallow are designed to demonstrate reflux more frequently or initiate disordered esophageal motility if esophagitis is present however both of these tests have a high false positive response which limits their usefulness[6] The presence of hiatal hernia on barium swallow has been found to correlate poorly with gastroesophageal reflux and is therefore not a significant aid to the clinician[8, 9] Functional integrity of the lower esophageal sphincter which prevents reflux of acid from the stomach into the esophagus and esophageal peristalsis which clears acid from the esophagus are the significant determinants of peptic esophagitis

Studies of the esophagus by barium swallow deserve special mention not only because they are the first studies needed in evaluating suspected esophageal disease but also because of recent improvements in technique[4] The most notable improvement in technique is the use of air contrast The earliest manifestations of esophagitis recognized with confidence are superficial erosions or ulcers Occasionally edema of the subtle transverse esophageal folds is noted Local areas of eccentric decreased distensibility or finely nodular mucosa are chronic changes Monilial esophagitis the most common infectious esophageal

From the Gast ointestinal Sect n f the Departm nt of Med ine Uni ersity of Pennsylvania School of M dicine at th Hosp tal of the Uni rs ty f Pennsyl ania Philadelphia P

Recei ed fo publicat on Oct 15 1979

Reprint req ests Sid ey Coh M D Gast intest n l Section Hosp t l of th U i rs ty f P nnsyl nia 3400 Spru e St Philad lphia Pa. 19104

000 8 03/80/100567 + 06$00 60 0 1980 The C V Mosby Co

this therapy as would be expected or if there are atypical features which suggest esophagitis of other etiologies then esophagoscopy often with biopsy or cytologic brushings is indicated If the barium swallow and esophageal manometry are typical of diffuse esophageal spasm and the Bernstein Test does not reproduce the patient's pain the patient may be treated with anticholinergics or nitrites without further investigation

Other organic disease

Although structural disease of the remainder of the gastrointestinal tract biliary tree pancreas liver, or peritoneal cavity may produce pain in the upper abdomen or lower chest these disorders often have features which distinguish them clinically from cardiac pain and they may be readily diagnosed if they are considered Ulcers within the stomach or duodenum occasionally cause lower chest pain, but the typical burning pain with relief following meals or antacids mandates the performance of an upper gastrointestinal x ray Occasionally a patient will have a superficial ulcer or gastritis in a normal stomach or an ulcer in an area difficult to evaluate radiographically (for instance an ulcer in a patient with a Bilroth II operation) and endoscopy reveals the pathology Biliary colic may cause pain in the high epigastrium and occurs within a few hours following a meal but may also be spontaneous Biliary colic is a misnomer since the pain is usually constant and lasts for one half hour to several hours The pain is often associated with nausea and vomiting and may radiate into the right scapula or right upper quadrant Acute cholecystitis may also cause high epigastric discomfort but is more likely to be associated with right upper quadrant pain and tenderness This pain is of longer duration than the pain of biliary colic and is associated with signs of inflammation such as leukocytosis or fever An oral cholecystogram or ultrasound of the gallbladder are reliable tests in over 95% of patients for the detection of gallstones Ultrasound is especially useful in the jaundiced patient Acute cholecystitis may be ruled out by gallbladder visualization on oral cholecystogram or gamma camera scanning following injection of one of the newer radionucleotides excreted in the bile

Acute pancreatitis pain radiates through into the back is persistent and usually is associated with an elevated serum amylase or urinary amylase clearance The pain of chronic pancreatitis is also persistent and penetrating to the back from the epigastric area with exacerbation following meals or drinking of alcohol Pseudocysts of the pancreas are notorious for their ability to present in unusual locations Dissection of a pseudocyst into the mediastinum may cause chest pain and dysphagia Chronic pseudocysts have been reported to have normal serum amylase in up to 50% of patients Occasionally pseudocysts may erode into the pleural space causing a pancreatic pleural fistula and generate chronic chest pain A chest x ray will show a pleural effusion especially on the left Endoscopic retrograde pancreatography is of value in diagnosing chronic pancreatic disease (small cysts chronic pancreatic fistula or carcinoma) and in assisting the surgeon in planning appropriate operative intervention Abdominal ultrasound or computerized tomography are other valuable noninvasive tests which detect pancreatic hepatic or subphrenic disease[3]

Functional gastrointestinal disorders causing chest pain

Motility disorders of the intestinal tract [illegible] biliary tree are more difficult to identify than [illegible] the structural disorders mentioned above Irritable bowel syndrome is now widely accepted as [illegible] distinct disorder which can be identified by specialized motility studies Recent investiga[illegible] have revealed that muscles of the large intestine in these patients have an abnormal myoelectric activity in the resting state with a predominant [illegible] of three cycle per minute activity in contrast [illegible] the normal predominance of six cycles per minute[31] These patients also show abnormal [illegible] prandial colonic spike potentials and co[illegible] tions[3] Normal individuals respond to a [illegible] containing fat by rapid increase in colonic [illegible] tractions which subside over an hour and a [illegible] Patients with irritable intestine on the o[illegible] hand demonstrate a delayed increase in [illegible] activity which peaks at a time when the [illegible] activity is decreasing Colonic motility stu[illegible] performed only in a few centers and under [illegible] circumstances we must rely upon exclu[illegible] structural disease and typical symptomat[illegible] Patients with irritable intestine character[illegible] are young adults with a chronic history of [illegible] abdominal pain exacerbated by meals The[illegible] experience diarrhea or constipation or both [illegible]

able I Diagnostic procedures to evaluate gastrointestinal causes of pain

Organ	*Suspected disorder*	*Primary tests*	*Secondary tests*
sophagus	Esophagitis	Barium swallow Esophageal manometery Esophagoscopy and biopsy Bernstein Test	pH probe Reflux scan
	Obstructive lesion	Barium swallow Esophagoscopy and biopsy	
	Motor disorder	Barium swallow Esophageal manometry Esophagoscopy	Cine-esophagogram Bernstein Test
tomach and intestine	Ulcer	Upper gastrointestinal series duodenoscopy	
	Irritable bowel	Barium enema Proctoscopy	Colonic motility studies
iliary tree	Gallstones	Oral cholecystogram Abdominal ultrasound	IV cholangiogram Biliary scan
	Dyskinesia	ERCP ? Sphincter of Oddi manometry	? Morphine test
ancreas	Acute or chronic disease	Serum amylase Abdominal echo or CAT ERCP	

ler of the esophagus esophageal manometry will give significant clinical information In achalasia peristalsis is absent and may be replaced by nonperistaltic (tertiary) waves The pressure of the lower esophageal sphincter is elevated and undergoes incomplete relaxation on swallowing

In diffuse esophageal spasm there are tertiary contractions of the esophagus but some peristaltic activity is preserved The tone of the lower esophageal sphincter may be normal or in some cases elevated and may simulate that seen in achalasia[2] Swallows of hot or cold liquids may precipitate tertiary contractions in these patients

Esophagoscopy is indicated in patients with achalasia not only because of the long term risk of carcinoma superimposed upon achalasia but because of the ability of carcinoma of the distal esophagus or adjacent structures which has invaded the esophageal nerves to mimic achalasia Patients in whom carcinoma is producing a idiographic and manometric picture identical to chalasia tend to be older to have symptoms for several months only and to have weight loss in xcess of that expected from the duration of their sophageal symptoms

The third type of chest pain of esophageal rigin is spontaneous chest pain caused by diffuse sophageal spasm The pain of spontaneous diffuse esophageal spasm is similar to the crushing substernal chest pain induced by eating in patients with odynophagia [1] Spontaneous esophageal chest pain is usually caused by an esophageal motor disorder It occasionally is a manifestation of carcinoma or esophagitis When the spontaneous esophageal spasms are the result of esophagitis appropriate therapy of the esophagitis may relieve the spasm and pain Patients whose esophageal spasm is a manifestation of a primary motor disorder may obtain relief by the use of nitroglycerin Symptomatic relief of esophageal pain by sublingual nitroglycerin simulates the response seen in cardiac pain Esophageal discomfort however is not brought on by exertion or relieved by rest Often the patients with spontaneous esophageal chest pain and spasm will have odynophagia or dysphagia The initial diagnostic test is a barium swallow as in the case of patients with heartburn or odynophagia Because these patients are most likely to *have a motor disorder especially diffuse esophageal spasm* esophageal manometry is usually the next procedure performed At the time of esophageal manometry it is often valuable to perform a Bernstein Test to reproduce the patient s symptoms if they are secondary to esophagitis If the barium swallow shows reflux from the stomach the Bernstein Test is positive and the lower esophageal sphincter pressure is reduced it is reasonable to treat such patients with antacids or cimetidine [3] If the patient does not respond

12 Benz, L., Hootkin, L. A., Margulies, S., Donner M W., Cauthorne R T., and Hendrix, T R A comparison of clinical measurements of gastroesophageal reflux, Gastroenterology 62 1 1972

13 Fisher R. S., Malmud L. S., Roberts G S., and Lobis I F Gastroesophageal (GE) scintiscan a new method to detect and quantitate GE reflux, Gastroenterology 70 301 1976

14 Ismail Beigi, F., Horton P F., and Pope C E Histological consequences of gastroesophageal reflux in man Gastroenterology 58 163 1970

15 Weinstein W M., Bogoch, E R., and Bowes K L. The normal human esophageal mucosa A histological reappraisal, Gastroenterology 68 40 1975

16 Price S F., Smithson K. W., and Castell D O Food sensitivity in reflux esophagitis Gastroenterology 75 240 1978

17 McNally E F., and Katz I The roentgen diagnosis of diffuse esophageal spasm Am J Roentgenol. 99 218 1967

18 Goldstein, H M., and Dodd, G D Double contrast examination of the esophagus, Gastrointest. Radiol. 1 3 1976

19 Fisher R S., and Cohen S Disorders of the lower esophageal sphincter Ann Rev Med. 26 373 1975

20 Vantrappen, G., Janssens, J., Hellemans J., and Coremans, G Achalasia diffuse esophageal spasm and related motility disorders, Gastroenterology 76 450 1979

21 Tucker H J Snape W J., and Cohen, S Achalasia secondary to carcinoma manometric and clinical features, Ann. Intern Med. 89 315 1978

22 DiMarino A. J., Jr., and Cohen S Characteristics of lower esophageal sphincter function in symptomatic diffuse esophageal spasm Gastroenterology 66 1 1974

23 Brand, D L. Martin D., and Pope C E Esophageal manometrics in patients with angina like chest pain Am J Dig Dis. 22 300 1974

24 Swamy N Esophageal spasm clinical and manometric response to nitroglycerine and long acting nitrites Gastroenterology 72 23 1977

25 Behar J Brand D L., Brown, F C., Castell, D O., Cohen S Crossley R S., Pope C E., and Winans C S Cimetidine in the treatment of symptomatic gastroesophageal reflux a double blind controlled trial, Gastroenterology 74 441 1978

26 Lapis, J L. Orlando R. C., Mittelstaedt C A., and Staab E V Ultrasonography in diagnosis of obstructive jaundice Ann Intern Med. 89 61 1978

27 Weissman H S Frank M S Bernstein, L. H and Freeman L M Rapid and accurate diagnosis of acute cholecystitis with 99m HIDA cholescintigraphy Am J Roentgenol. 132 523 1979

28 Cameron J L. Chronic pancreatic ascites and pancreatic pleural effusions Gastroenterology 74 [illegible]

29 Cotton P B Progress report ERCP [illegible] 1977

30 Korobkin M Gallium ultrasound, and computed tomography in the evaluation of suspected abdominal abscess, in Computed Tomography Ultrasound [illegible] ray An Integrated Approach, edited by M F [illegible] San Francisco 1978 University of California Press

31 Snape W J., Carlson, G M and Cohen, [illegible] myoelectric activity in the irritable bowel [illegible] Gastroenterology 70 376 1976

32 Sullivan M A., Cohen, S and Snape W J [illegible] myoelectric activity in irritable bowel syndrome [illegible] eating and anticholinergics, N Engl J Med [illegible] 1978

33 Freeman J B Cohen, W N and DeBerg [illegible] Cholecystokinin cholangiography and analysis of duodenal bile in the investigation of pain in the right upper quadrant of the abdomen without gallstones [illegible] Gynecol. Obstet. 140 371 1975

34 Goldstein F Grunt R., and Margulies, M Cholecystokinin cholecystography in the differential diagnosis of acalculous gallbladder disease Am. J Dig Dis. [illegible] 1974

35 Berk, R N Cholecystokinin cholecystography in the diagnosis of chronic acalculous cholecystitis and [illegible] dyskinesia, Gastrointestinal Radiol. 1 [illegible]

36 Thompson W M and Amberg J R. [illegible] C terminal octapeptide of of cholecystokinin [illegible] radiology Gastrointest Radiol. 3 191 [illegible]

37 Bodvall B The postcholecystectomy syndrome [illegible] Clinics in Gastroenterology January 1973 W B [Saun]ders Company p 103

38 O[illegible]nes M., Gronseth K Larsen S Lo[illegible] T [illegible] and Nordshus, T Comparison of endoscopic [illegible] and intravenous cholangiography in diagnosis of [illegible] calculi, Lancet 2 [illegible] 19[illegible]

39 Bar Meir S Greenen, J E., Hogan, W J Dodds W [illegible] Stewart E T., and Arndorfer R. C., Biliary and pancreatic duct pressures measured by ERCP [illegible] patients with suspected papillary stenosis Dig Dis 24 209 1979

40 Nardi, G L. Papillitis and stenosis of the sphincter of Oddi, Surg Clin North Am 53 1149 1973

41 Steinberg, W M., Toskes P P and [illegible] Nonspecificity of the morphine prostigmin test Gastroenterology 76 1255 1979

42 LoGiudice J A Geenen J E., Hogan, W J and [illegible] W J Efficacy of the morphine-prostigmin test [illegible] evaluating patients with suspected papillary stenosis Dig Dis Sciences 24 455 1979

notice mucus on the bowel movement Most patients have lower abdominal crampy pain but patients with the so called splenic flexure syndrome have left upper quadrant pain which may radiate to the shoulder In order to establish a diagnosis of irritable intestine one must first exclude other diseases with a normal upper intestinal x ray and barium enema In addition most clinicians insist upon a normal proctoscopic examination and no evidence of inflammation on white blood count or erythrocyte sedimentation rate The pain and bowel irregularities of these patients may respond to low fat high fiber diet and to anticholinergic therapy

Biliary dyskinesia is a poorly documented phenomenon for which there is beginning to emerge objective evidence The pain of these patients mimics biliary colic but gallstones or structural abnormality are not found[7] If the gallbladder is present it empties poorly in response to intravenous cholecystokinin infusion or fatty meal and the characteristic pain is reproduced Some investigators have noted the gallbladder to distend as if straining to empty against a resistance There is controversy regarding the significance of these findings and surgical therapy must be undertaken with great caution Poor gallbladder emptying is also seen in diabetic and post vagotomy patients but does not cause symptoms

Another group of patients with suspected biliary dyskinesia are those who have previously undergone a cholecystectomy but present with similar biliary symptoms[7] Good visualization of the bile duct is essential to document the absence of organic disease Intravenous cholangiography has a high false negative rate and retrograde transhepatic or operative cholangiography is needed[3] Recent and as yet unconfirmed evidence suggests that these patients have an elevated sphincter of Oddi pressure determined during endoscopic retrograde cannulation The bile duct may be slightly dilated and the radiographic dye may drain slowly Others have advocated the use of a morphine and cholinergic stimulation test which reproduces the patient s pain and causes elevated serum amylase lipase or liver enzymes[4] The value of this provocative test has been questioned by findings that normal volunteers may also have an increase in these enzymes or experience pain following morphine and cholinergic stimulation Although it remains difficult to obtain objective evidence of post cholecystectomy biliary dyskinesia some centers have reported beneficial effects of sphincteroplasty especially when the septum between the bile duct and pancreatic duct is divided Long follow up of patients chosen for sphincteroplasty because of abnormal sphincter pressure is not yet available Sphincteroplasty is difficult has significant morbidity and must be undertaken only following the most careful clinical assessment When surgery is performed on the bile duct the surgeon may describe a thickened septum between a common bile duct and the pancreatic duct Medical therapies which have been tried in these patients include anticholinergics long acting nitrites and low fat diets As is the case with gallstone patients most of the patients are female and they often have had symptoms for a prolonged period prior to cholecystectomy

In summary various gastrointestinal disorders may cause chest pain In most cases a distinction between these disorders and cardiac disease can be made by history The most difficult condition to distinguish from cardiac disease is symptomatic diffuse esophageal spasm but history barium swallow and especially esophageal manometry have now allowed an easier distinction to be made

REFERENCES

1 Henderson R D Wigle E D Sample K, and Marryatt G Atypical chest pain of cardiac and esophageal origin Chest 73 24 19 8
2 Brand D L Martin D and Pope C E Esophageal manometrics in patients with angina like chest pain Am J Dig Dis 22 300 19 /
3 Battle W S Nyhus L M, and Bombeck C T Gastroesophageal reflux Diagnosis and treatment Ann Surg 177 560 19"3
4 Laufer I Double Contrast Gastrointestinal Radiology—With Endoscopic Correlation Philadelphia, 19 9 W B Saunders Company
5 Pope C Viewpoints Digestive Disease 4 1 19"2
6 Stilson W L Sanders I Gardiner G A Gorman H C and Lodge D F Hiatal hernia and gastroesophageal reflux Radiol 93 1323 1969
7 Donner M W Silbiger M L Hookman, P, and Hendrix T R Acid barium swallows in the radiographic evaluation of clinical esophagitis Radiology 87 220 1966
8 Cohen S and Harris L Does hiatus hernia affect competence of the lower esophageal sphincter? N Engl J Med 284 1053 19"1
9 Dyer N, and Pridie R Incidence of hiatus hernia in asymptomatic patients Gut 9 696 1968
10 Winans C and Harris L Quantitation of lower esophageal sphincter strength, Gastroenterology 52 " 3 19"
11 Behar J Biancani, P, and Sheahan D G Evaluation of esophageal tests in the diagnosis of reflux esophagitis Gastroenterology 71 9 19"6

reach or decrease below the 95th percentile of the age group of the patient we proceed with drug treatment Our mean values for plasma cholesterol levels and the 95th percentile cutting points are given in Table I Our 95th percentile for plasma triglycerides is 200 mg %

The drugs presently available on the market are few in number have limited efficacy, and may have multiple side effects Instead of being complete or exhaustive I shall restrict myself to the description of those drugs that are the most effective or the most widely used for the treatment of hyperlipidemia

Clofibrate (CPIB) Ethyl p chlorophenoxysobutyrate (CPIB) is a branched chain fatty acid ester

Indications Clofibrate is the drug of choice in the treatment of hypertriglyceridemia Many patients with combined hyperlipidemia also respond

Effect Clofibrate reduces plasma triglyceride levels by about 30% to 40% and plasma cholesterol levels by 5% to 15% In hypertriglyceridemic patients LDL and HDL concentrations increase and VLDL decreases The response in hypercholesterolemia is poor

Mechanism of action Sterol balance measurements indicated a significant increase of the fecal excretion of cholesterol end products (neutral sterols)[5] and a decrease of cholesterol absorption[6] during clofibrate administration inducing a negative sterol balance (more cholesterol end products coming out than cholesterol going in) The action on triglycerides seems to be both a decrease of VLDL production and acceleration of its catabolism to LDL Or simply endogenous triglycerides are synthesized slower by the liver and once made they are broken down faster

Side effects Nausea and diarrhea may rarely occur We have seen a few cases of myalgia with elevated CPK levels returning to normal after cessation of drug administration It has been shown that the drug produces lithogenic bile and both the CDI and the WHO study[2] demonstrated increased rates of cholelithiasis and diseases of the biliary tract in patients receiving clofibrate

Drug interact[illegible] Clofibrate increases the effect of coum[illegible] anticoagulants Patients should be carefull[illegible] monitored on both medications

Dose and costs Dose is 500 mg capsules four times daily (or two capsules twice a d[illegible] January 1980 the cost *to our pharmac[illegible]* was [illegible] per 100 capsules

Cholestyramine and colestipol [illegible] unabsorbable high molecular weight [illegible] exchange resins

Indications The drug of choice in hyperch[illegible]terolemia and the drug to be used in ch[illegible] when drug treatment is indicated

Effect These compounds reduce plasma ch[illegible]terol levels by about 20% to 30% Plasma trig[illegible]erides may moderately increase during [illegible] administration LDL cholesterol is decrea[illegible] VLDL triglycerides may moderately incr[illegible] and HDL remains unchanged[7,8]

Mechanism of action Cholestyramine [illegible] colestipol bind bile acids in the gastrointe[illegible] tract, thereby interrupting the enterohepatic c[illegible]culation Bile acids are an important end pro[illegible] of cholesterol metabolism and their incre[illegible] fecal excretion leads to a more rapid convers[illegible] cholesterol to bile acids which significa[illegible] decreases the plasma cholesterol concentra[illegible] Cholesterol absorption is somewhat decrea[illegible] but only if the drug is taken *before* meals[9]

Side effects Constipation is the most freque[illegible]ly seen complication sometimes improved [illegible] the use of stool softeners The taste and con[illegible]tency of the resins which are not soluble in w[illegible] may also be unpleasant

Drug interactions It may reduce the abs[illegible]tion of a number of compounds (digitalis [illegible] soluble vitamins iron thyroid preparat[illegible] tetracycline thiazides etc) It is recomme[illegible] that any other medication be taken at leas[illegible] hour before the resins

Dose and costs Begin with one 4 gm sa[illegible] *before* each meal (three times daily) and th[illegible] may be doubled or even tripled in adults [illegible] January 1980 the cost *to our pharmac[illegible]* [illegible] $48 18 per 100 sachets

Nicotinic acid This is a vitamin of the B g[illegible] (niacin) which prevents pellagra given in [illegible] larger doses to reduce plasma lipids

Indications Nicotinic acid is the only [illegible]lowering drug which is highly effective in red[illegible] both plasma cholesterol and triglyceride lev[illegible] is indicated in hypercholesterolemia hyper[illegible]glyceridemia and combined hyperlipidem[illegible] [illegible]sibly in combination with other drugs (see Ta[illegible] III)

Effect Nicotinic acid lowers plasma chole[illegible]

rug treatment of hyperlıpıdemıa

ɜul Samuel M D
-w York N Y

'urıng the past decade we have wıtnessed one of ıe major controversıes of modern pharmacology ı the field of drugs used for the treatment of yperlıpıdemıa First as ıs frequently the case ıe lapse of tıme ımproved methodology and the dvent of large clınıcal trıals have demonstrated gnıficant and hıtherto unsuspected sıde effects f a number of drugs wıdely used ın the field lofibrate was shown to ınduce gallstone forma ıon[1,2] d thyroxın caused sıgnıficant cardıac rrhythmıas[3] estrogens ıncreased thromboem olıc complıcatıons[3] just to mentıon a few Sec nd the valıdıty of drug ınterventıon ıtself has ecome the subject of controversy and has been erıously questıoned The results of the Coronary Drug Project and of the World Health Organıza ıon trıal[?] showıng no dıfference ın cardıovascular nortalıty rate between patıents ın the control and drug treatment groups have raısed concerns ıbout the valıdıty and efficacy of drug treatment n thıs field

Justıfiably the questıon has to be asked what re we treatıng numbers or people?

And yet despıte the controversy we are faced vıth more and more evıdence whıch ındıcates hat ıncreased plasma lıpıd levels are a sıgnıficant ıealth hazard and ought to be reduced by what ver means The epıdemıologıc evıdence ıs over vhelmıng ındıcatıng ıncreased rısk of cardıovas 'ular dısease as plasma lıpıds go up Concernıng he clınıcal trıals the reductıon of plasma choles erol levels ın the CDP was only 6% wıth clofibrate one would really not expect too much of that Conversely ın the WHO study there was a sıgnıficant reductıon ın the ıncıdence of nonfatal myocardıal ınfarctıon yet thıs result was obtaıned wıth only a 9% reductıon of serum cholesterol levels (Sımılar results were seen wıth nıcotınıc acıd ın the CDP) Moreover ın the WHO study the reductıon of myocardıal ınfarc tıon ın the clofibrate treated group was most marked ın men who experıenced the largest reductıons ın plasma cholesterol levels Thus the results of the WHO study offer the first clear cut support for the lıpıd hypothesıs whıch postu lates that reducıng plasma cholesterol by what ever means should lead to a lower ıncıdence of cardıovascular morbıdıty and mortalıty

Table I Average plasma cholesterol concentra tıons and 95th percentıles accordıng to age

Age (years)	Mean plasma cholesterol	95th percentıle (mg %)
12 17	1ı6	228
21 29	193	260
30-39	212	2̅0
40-49	228	280
50-59	230	290

U S Dept of HEW
Center for the Prevent on of Prem ture Arterıoscl rosıs Rock f ller Unı rs ty

Whom to treat?

The prımary treatment of hyperlıpıdemıa ıs dıetary The precedıng artıcle descrıbes ıts modal ıtıes ın detaıl But who should be treated wıth drugs and wıth what drugs? At the outpatıent clınıc of The Rockefeller Unıversıty Hospıtal our guıdelıne ıs to ınıtıally ınstıtute dıetary treatment for not less than three months If at the end of that perıod plasma lıpıd levels have faıled to

rom The Rock fell Unıversıty New York Cıty and The Long sl nd Jewısh Hıllsıd Med cal Center New Hyd Park, N Y

upported ın part by Un ted States P bl c Health Servıce gra ts HL-22ɜ67 and HL-06222 from th N t o l Heart Lu g a d Blood Instıtute and by grant No FR-0010? from th General Clınıcal Research Centers Branch of the Dıvısı n f Research Resources.

Receıved f publıcatıon J e 6, 1980

Reprınt req ests Paul Sam l, M D Th Rock f ll Unıversıty 1230 Yo k A e New York N Y 100?1

reach or decrease below the 95th percentile of the age group of the patient we proceed with drug treatment Our mean values for plasma cholesterol levels and the 95th percentile cutting points are given in Table I Our 95th percentile for plasma triglycerides is 200 mg %

The drugs presently available on the market are few in number, have limited efficacy, and may have multiple side effects Instead of being complete or exhaustive, I shall restrict myself to the description of those drugs that are the most effective or the most widely used for the treatment of hyperlipidemia

Clofibrate (CPIB) Ethyl p chlorophenoxysobutyrate (CPIB) is a branched chain fatty acid ester

Indications Clofibrate is the drug of choice in the treatment of hypertriglyceridemia Many patients with combined hyperlipidemia also respond

Effect Clofibrate reduces plasma triglyceride levels by about 30% to 40% and plasma cholesterol levels by 5% to 15% In hypertriglyceridemic patients LDL and HDL concentrations increase and VLDL decreases[4] The response in hypercholesterolemia is poor

Mechanism of action Sterol balance measurements indicated a significant increase of the fecal excretion of cholesterol end products (neutral sterols)[5] and a decrease of cholesterol absorption[6] during clofibrate administration inducing a negative sterol balance (more cholesterol end products coming out than cholesterol going in) The action on triglycerides seems to be both a decrease of VLDL production and acceleration of its catabolism to LDL Or simply endogenous triglycerides are synthesized slower by the liver and once made they are broken down faster

Side effects Nausea and diarrhea may rarely occur We have seen a few cases of myalgia with elevated CPK levels returning to normal after cessation of drug administration It has been shown that the drug produces lithogenic bile and both the CDP[1] and the WHO study[2] demonstrated increased rates of cholelithiasis and diseases of the biliary tract in patients receiving clofibrate

Drug interactions Clofibrate increases the effect of coumarin anticoagulants Patients should be carefully monitored on both medications

Dose and costs Dose is 500 mg capsules four times daily (or two capsules twice a da[illegible] January 1980 the cost *to our pharmacy* [illegible] per 100 capsules

Cholestyramine and colestipol [illegible] unabsorbable high molecular weight [illegible] exchange resins

Indications The drug of choice in hyper[illegible] terolemia and the drug to be used in ch[illegible] when drug treatment is indicated

Effect These compounds reduce plasma ch[illegible] terol levels by about 20% to 30% Plasma tri[illegible] erides may moderately increase during [illegible] administration LDL cholesterol is decrea[illegible] VLDL triglycerides may moderately incre[illegible] and HDL remains unchanged[7,8]

Mechanism of action Cholestyramine [illegible] colestipol bind bile acids in the gastrointest[illegible] tract thereby interrupting the enterohepatic c[illegible] culation Bile acids are an important end pro[illegible] of cholesterol metabolism and their incre[illegible] fecal excretion leads to a more rapid conver[illegible] cholesterol to bile acids which significa[illegible] decreases the plasma cholesterol concentra[illegible] Cholesterol absorption is somewhat decrea[illegible] but only if the drug is taken *before* meals[4]

Side effects Constipation is the most frequ[illegible] ly seen complication sometimes improved [illegible] the use of stool softeners The taste and con[illegible] tency of the resins which are not soluble in wa[illegible] may also be unpleasant

Drug interactions It may reduce the ab[illegible] tion of a number of compounds (digitalis [illegible] soluble vitamins iron thyroid preparatio[illegible] tetracycline thiazides etc) It is recommen[illegible] that any other medication be taken at least [illegible] hour before the resins

Dose and costs Begin with one 4 gm. s[illegible] *before* each meal (three times daily) and this [illegible] may be doubled or even tripled in adults [illegible] January 1980 the cost *to our pharmac*[illegible] $48 18 per 100 sachets

Nicotinic acid This is a vitamin of the B [illegible] (niacin) which prevents pellagra given in [illegible] larger doses to reduce plasma lipids.

Indications Nicotinic acid is the only [illegible] lowering drug which is highly effective in re[illegible] both plasma cholesterol and triglyceride leve[illegible] is indicated in hypercholesterolemia hyper[illegible] glyceridemia and combined hyperlipidemia, p[illegible] sibly in combination with other drugs (see Ta[illegible] III)

Effect Nicotinic acid lowers plasma choles[illegible]

Table II Effect of clofibrate neomycin and colestipol therapy on body masses of cholesterol

Study	n	Ma (gm)	M (gm)	M Ma† (gm)
Control		38	109	71
Clofibrate	5	28	77	49
Difference (%) (Ref 5)		10 (26)	32 (?9)	22 (31)
Control		36	103	67
Neomycin	4	22	0	48
Difference (%) (Ref 16)		14 (39)	33 (3?)	19 (28)
Control		24	5?	31
Colestipol	7	23	55	32
Difference (%) (Ref 17)		—	—	—

Ma = Rapidly exchangeable pool of cholesterol (Plasma + RBC + liver + gut)
M = Minimum estimate of total body mass of cholesterol (except CNS).
† M = Slowly turning over masses or tissue cholesterol.

vels by about 8% to 16% and triglycerides by ?% to 30% It lowers plasma free fatty acids VLDL and LDL and it increases HDL levels[8]

Mechanism of action It is frequently stated to be unknown Nicotinic acid was shown to decrease lipolysis decrease the hepatic production of triglycerides and increase fecal excretion of cholesterol end products (neutral sterols)

Side effects are unfortunately numerous and patient acceptance is poor It seems to me that for this reason the drug is only a second line compound The main problem is intense cutaneous flushing and pruritus Starting with small doses (100 mg in the middle of meals) and increasing the dose gradually may somewhat alleviate this symptom Anorexia nausea vomiting diarrhea and activation of peptic ulcer have been reported Glucose intolerance impaired liver function tests and hyperuricemia may also occur

Drug interactions May potentiate the effect of vasodilator drugs or hyperuricemic diuretics

Dose and costs Begin with 100 mg tablets three times daily and increase gradually to one gram (two 500 mg tablets) in the middle of three meals (3 gm per day) In January 1980 the cost to our pharmacy was $1 50 per 100 (500 mg) tablets

Neomycin Neomycin is a broad spectrum aminoglycoside antibiotic poorly absorbed from the gastrointestinal tract (< 3%) It lowers plasma cholesterol levels at very low doses of administration (0.5 to 2 gm daily)

Indications Hypercholesterolemia

Effect The drug reduces plasma cholesterol levels by 20% to 30% sometimes even in patients with resistent familial hypercholesterolemia[6]

Mechanism of action Neomycin decreases cholesterol absorption and increases fecal cholesterol end product (neutral sterol) excretion leading to a negative sterol balance[1] Its effect may be mediated through its action on the intestinal bacterial flora (markedly decreased 7α-dehydroxylase activity of intestinal bacteria) or by interfering with micelle formation in the lumen of the gastrointestinal tract

Side effects One third to half of patients on neomycin have transitory diarrhea or abdominal cramps that usually subside after 1 or 2 weeks Lomotil is helpful for this symptom The small amounts of neomycin absorbed from the gut are excreted by the kidney thus normal renal function is an absolute prerequisite for using the drug Ototoxicity has been reported in very rare cases we perform periodic hearing tests in patients treated with neomycin At higher dose levels (12 gm daily) steatorrhea renal damage staphylococcus enterocolitis moniliasis and multiresistant coliform overgrowth have been reported however we have not observed these complications with the small doses used for cholesterol reducing purposes[12]

Drug interactions Digoxin should be administered one hour before neomycin is given inasmuch as there may be interference with its absorption The possibility exists that coumarin anticoagulants may be potentiated by the drug

Dose and costs Tablets of 0.5 gm of neomycin sulfate three or four times daily after meals (two

Annotations

Coxsackieviruses and chronic valvular heart disease

Acute rheumatic carditis of streptococcal etiology is considered to be the predominant cause of chronic valvular heart disease (CVHD). Hence there is a tendency to assume that all or most cases of CVHD are of rheumatic origin. This has resulted in an inadequate search for other possible etiological factors in CVHD.

It is now clear that several infectious agents can cause endocarditis and valvulitis in man and animals. These agents are group B coxsackieviruses (CBV), adenovirus, encephalomyocarditis virus, virus III, inflammatory fibroma virus, vaccinia virus, pseudorabies virus, varicella virus, *Chlamydia psittaci*, *Coxiella burnetii*, and *Mycoplasma gallisepticum*. Among these CBV form an important group.

The relationship between viruses and CVHD may be investigated (1) in experimental animal models, (2) by following up the clinical course of individuals with viral myocarditis, and (3) by investigating patients with CVHD.

Endocarditis and valvulitis are caused by CBV infection in mice and in cynomolgus monkeys. They also cause CVHD in cynomolgus monkeys with pathological changes similar to those of human rheumatic heart disease.

In human viral myocarditis the cardiac valves may be affected either directly as a result of valvulitis or indirectly by the involvement of the valve ring and the valve apparatus due to cardiac dilatation. It would be reasonable to assume that the more severe the myocarditis, the greater the likelihood of valvulitis and consequent CVHD. However, an evaluation of the published reports of the follow up of patients with viral myocarditis has been difficult because the data available are incomplete. Babb and colleagues reported on four patients ranging in age from 4 to 19 months with CBV myocarditis. A 1? month old child had no murmur on the phonocardiogram and only a slight cardiac enlargement seen on the chest x ray at the time of his acute illness. However, this child had an apical systolic murmur without cardiac failure 4 months later. The second patient, a 9 month old infant, had a normal chest x ray and ECG, but the phonocardiogram showed a mid dia[illegible] murmur of the ejection type [illegible] the acute illness. Five months later there was still a slight [illegible] murmur. The third patient was a 4 month old infant wh[illegible] chest x ray and ECG but wa[illegible] had a blowing systolic murmur. Th[illegible] the twelfth day and the child wa[illegible] well [illegible] evidence of [illegible] [illegible]rth patient had no [illegible]

Smith report[illegible] [illegible]BV myocarditis four of whom had [illegible] these patients had enlarged hearts an[illegible] third had only an abnormal ECG [illegible] had a pansystolic murmur followed [illegible] short mid-diastolic murmur presumed [illegible] viral infection. This patient was later admitted for a proved viral myocar[illegible] to CBV type 4. There is no mention of perm[illegible] damage during follow up. In a later repor[illegible] there were ?3 with myocarditis and residual card[illegible] with or without mitral incompetence.[illegible] Clinical deta[illegible] ing admission were incomplete.

Sainani and co workers[illegible] have reported on [illegible] proved CBV myocarditis of whom eight had [illegible] murmurs including one with an apical mid-dia[illegible]. There was diffuse cardiac enlargement in 1? cases [illegible] clinico radiological correlations were given. Of the [illegible] followed up, one had a systolic murmur f[illegible] another for 19 months and a third had a [illegible] mid-diastolic murmur for 6 months. In a later [illegible] India there were 19 patients with CBV myocard[illegible] whom 13 had Grade 2/6 apical systolic murmurs [illegible] acute stage. None of them had murmurs during [illegible] up.

Bengtsson studied 90 patients with cardiac [illegible] following infectious diseases, of whom ?4 had a variety of infections. A systolic murmur was present in [illegible] patient had diastolic murmurs. The persistence of [illegible] involvement is not mentioned in their report.

Gerzen et al.[illegible] reported on the follow up of [illegible] acute myocarditis, ? of whom had a viral etiolog[illegible] them had evidence of valvular involvement.

Thus the reports on patients with CBV myocard[illegible] that valvular involvement in the acute phase [illegible] quent. However, the follow up reports do not give [illegible] picture of the frequency of CVHD. Myocarditis d[illegible] viruses seems to be less often associated with val[illegible] ment.

Burch and colleagues,[illegible] using immunofluorescent [illegible] nique studied 5? routinely autopsied hearts. CBV [illegible] were found in the myocardium in 30.9% and in the [illegible] dium and valve in 5.45%. The prevalence was [illegible] children than in adults. Later Burch and Colcolough [illegible] onstrated CBV type 4 antigen in the areas of [illegible] damage including the aortic valve in a pa[illegible] regurgitation, myocarditis and nephritis.

Ward and Ward examined left atrial and [illegible] specimens from patients with CVHD by [illegible] flourescence for the presence of antigens of a variety of [illegible] (polio types 1 3, influenza A, echo type 16, CBV [illegible] *Chlamydia psittaci* and *Mycoplasma pne[illegible]* [illegible] antigen was found in one or more cases. [illegible] positive for two or three unrelated antigens. There [illegible] difference in the frequency of detection of a[illegible] with and without a history of rheumatic fever.

Thus the investigations on patients with CVHD g[illegible] support to a possible virus etiology in val[illegible] Further evidence for CBV involvement in the [illegible]

000?-8 03 80 100 ?8 + 03500.30 0 © 1980 The C[illegible]

cessity of individual judgment in this field is —nment

It is clear from the foregoing that in most —tients we can lower plasma lipids by drugs ugs which may have side effects Thus the risk d benefits must be carefully weighed

ERENCES

1 The Coronary Drug Project Research Group Clofibrate and niacin in coronary heart disease J.A M A 231 360 19ı⌄

Committee of Principal Investigators A cooperative trial in the primary prevention of ischaemic heart disease using clofibrate Br Heart J 40 1069 19/8

The Coronary Drug Project Research Group Initial findings leading to modifications of its research protocol J.A.M.A 214 1303 1970

Wilson D E and Lees R S Metabolic relationship among the plasma lipoproteins, J Clin Invest 51 1051 1972.

Grundy S M., Ahrens E H Jr Salen G Schreibman P H and Nestel P J Mechanism of action of clofibrate on cholesterol metabolism in patient with hyperlipidemia J Lipid Res. 13 531 1972

Davidson N O McNamara D J Samuel, P and Ahrens E H Jr Cholesterol absorption (%) is altered by lipid lowering drugs but not by diet Circulation 59 and 60(Suppl II) II 32 1979

Glueck C J Ford S Jr Scheel D and Steiner P Colestipol and cholestyramine resin comparative effects in familial Type II hyperlipoproteinemia J.A M.A 222 6 6 197?

Witztum, J L. Schonfeld G and Weldman S W The effect of colestipol on the metabolism of very low-density lipoproteins in man J Lab Clin Med 88 1008 1976

9 Shepherd J Packard C J Patsch J R., Gotto A M., Jr., and Taunton O D Effects of nicotinic acid therapy on plasma high density lipoprotein subfraction distribution and composition and on apolipoprotein A metabolism J Clin Invest 63 8?8 1979

10 Samuel, P Holtzman C M., and Goldstein J Long term reduction of serum cholesterol levels of patients with atherosclerosis by small doses of neomycin Circulation 35 938 1967

11 Sedeghat H Samuel P Crouse J R., and Ahrens, E. H Jr Effect of neomycin on absorption synthesis and/or flux of cholesterol in man J Clin Invest 55 12 1975

12 Samuel P Current Concepts Treatment of hypercholesterolemia with neomycin A time for reappraisal, New Engl J Med 301 595 1979

13 Lelorier J Dubreuil Quidoz S., Lussier-Cacan S Huang Y S., and Davignon J Diet and probucol in lowering cholesterol concentrations, Arch Intern Med 137 1429 197

14 Samuel P and Lieberman S Improved estimation of body masses and turnover of cholesterol by computerized input-output analysis, J Lipid Res 14 189 1973

15 Goodman D S., Noble R. P., and Dell, R B Three pool model of the long term turnover and plasma cholesterol in man J Lipid Res. 14 178 1973

16 Samuel P Holtzman C M Meilman E., and Perl W Effect of neomycin on exchangeable pools of cholesterol in the steady state J Clin Invest 47 1806 1968

17 Goodman D S., Noble R P., and Dell R B The effects of colestipol resin and of colestipol plus clofibrate on the turnover of plasma cholesterol in man J Clin Invest 52 ?646 1973

23 Babb J M Stoneman M E R and Stern H Myocarditis and croup caused by Coxsackievirus type B5 Arch Dis Child 36 551 1961

24 Smith W G Adult heart disease due to Coxsackievirus group B Br Heart J 28 204 1966

25 Smith W G Coxsackie B myopericarditis in adults AM HEART J 80 34 1970

26 Sainani G S Krompotic E and Slodki S J Adult heart disease due to Coxsackievirus B infection Medicine 47 133 1968

27 Sainani G S Dekate M P and Rao C P Heart disease caused by Coxsackie virus B infection Br Heart J 37 819 1975

28 Bengtsson E Acute myocarditis and its consequences in Sweden Postgrad Med J 48 754 1972

29 Gerzen P Granath B Holmgren B and Zetterquist S Acute myocarditis—A followup study Br Heart J 34 575 1972

30 Burch G E Sun S C Colcolough H L Sohal R S and DePasquale N P Coxsackie B virus ... and valvulitis identified in routine autopsy spec... immunofluorescent techniques AM HEART J ... 1967

31 Burch G E and Colcolough H L Progressive Coxsackieviral pancarditis and nephritis Ann I... 71 963 1969

32 Ward C and Ward A M Virus antigen ... in valvular heart disease Lancet 1 ... 19...

33 Chandy K G John T J Mukundan P ... G Coxsackie B antibodies in rheumatic ... disease Lancet 1 381 1979

34 Vendsborg P Hansen L and Olsen K ... incidence of a history of acute rheumatic fever ... rheumatic heart disease Cardiol ... 1968 (Cited in Ref 35)

35 Pomerance A and Davies M J editors The P... of the Heart ed 1 Oxford 19... Blackwell Sci... Publications p 307

Cardiopulmonary resuscitation—an element of sophistication in the 18th century

Drowning or near drowning accidents appear to have been as prevalent in the 1700s as they are today Interest in the aggressive treatment of drowning or near-drowning victims has always been great for these individuals were usually in good health and because it has become apparent that survival is possible even after as long as 40 minutes below the surface Eighteenth century reports of survivals after hours under water have been noted but of course would be difficult or impossible to confirm During the latter half of the 18th century however elements of the pathophysiology of drowning were recognized Hosack discusses popular opinions by "distinguished writers" on the subject that in essence point to the primacy of hypoxemia— it is probable that the death which ensues or seems to ensue in drowned persons is entirely owing to the stopping of respiration and to the ceasing in consequence of the circulation of the blood Laryngospasm was also recognized— a contraction of parts about the larynx preventing the air from passing into or out of the lungs The lack of significant amounts of water in the lungs of some individuals ... was also known

The interest ... for providing assistance to the drowning ... the establishment of societies in the ... (Humane Societies) first in Amsterdam then in ... European capitals and finally in the United ... societies which were also concerned with ... death procured books and manuscripts ... resuscitation procured and kept in good ord... published medical advice on related ... all successful and unsuccessfully tr... in essence stimulated research and new appr... treatment ... prizes and monetary grants to th... contributions to the already existing knowledge ... It was claimed by Hosack that nearly one thousand persons were ... from death in a 20 year period by the societies in ... and London

A clear concise approach to the management ... ment of the victims of drowning (near-drowning) was ... lished by the Humane Society of the State of New Y... well as by Hosack These same therapeutic princip... reviewed about ten years later in a chapter of the ... Reece Early attention to potential hypotherm... was ... nized The rapid reestablishment of respirati... Mouth to mouth or mouth to nose approaches to inflate the lungs were suggested though a bellows was ... used Hosack favored inserting a tube into the trachea ... which tube a bellows was connected an approach ... similar to our present-day effort He noted that ... approach allowed air to be thrown directly int... the ... whereas other methods were associated with passage ... into the stomach He made note of one objection to ... the bellows namely that it had to be removed a... inflation Though mouth to mouth or mouth to nose ... tion was apparently used at that time he mistaken... the air "blown in from the lungs of another person ... impure and therefore must render the blood ... circulation than before" Hosack reviews ... tracheal intubation and claimed that one of ... would be that it spared the patient bronchotomy ... as air may thereby be thrown into the lungs as ... by an opening into the wind pipe

Lack of response to the above resuscitative ef... ly was recognized as being related to cardiac ... Modern reviews of the subject of drowning ... potential cardiac arrhythmias and conduction ... could be related to the hypoxemia and ...

0002-8703/80/100...+... © 1980 The C. V. M...

ble I Geometric mean titers of antibody to
up B coxsackieviruses

	Type					
	B1	B2	B3	B4	B5	B6
-matched control (n = 58)	13	16	11	18	10	8
HD with h/o R F (n = 12)	14	26	33	49	10	14
HD without h/o R F (n = 16)	8	26	44	74	8	12

o R.F = history of rheum tic fe er CVHD = chronic valvular
rt disease

HD was the subject of a recent preliminary report by us a from 29 patients with mitral stenosis and from 58 matched controls were examined for the prevalence and rs of neutralizing antibodies to CBV types 1 6 There e statistically highly significant differences between ients and controls in the titers of antibody to CBV type 3 l 4 and in the prevalence of antibody to type 3 Among the ients 12 had a previous history of rheumatic fever and 16 not In one patient the history was equivocal The metric mean titers of antibodies in these patients are wn in Table I Clearly the mean titers of antibody to CBV es 3 and 4 were considerably higher in patients without a tory of rheumatic fever than in those with such history

some patients with CVHD do not have a history of eumatic fever While there has been a reported decline in prevalence of acute rheumatism and consequent CVHD decline in the prevalence of CVHD without preceding umatic fever has been observed This further supports the ncept of nonrheumatic CVHD which is embodied in newer rms such as "rheumatic type" valvular deformity and rus valvular heart disease

It is also possible that in some cases of CVHD the valve formity may be the result of damage produced by sequential t subclinical attacks of rheumatic and/or virus valvulitis rhaps such valvular deformity is more commonly stenotic her than regurgitant for the following reasons It is the tient with mild rheumatic carditis who is more likely to velop a stenotic valvular lesion On the contrary those with rurgitant valvular deformities more often give a history of eceding severe rheumatic carditis It is also known that tients with stenotic valvular lesions give a history of acute eumatism less often than those with regurgitant valvular sease

More intensive studies on a large number of patients with notic and regurgitant valve deformities and a follow up of ose with proved viral myocarditis for evidence of presistent lvular disease may result in a change of our present owledge on the etiological factors responsible for chronic lvular heart disease

K George Chandy
T Jacob John
George Cherian
Cardiology and Virology Departments
Christian Medical College Hospital
Vellore 632004 India

EFERENCES

Ward C Virus valvular heart disease AM HEART J 90 804 1975
2 Burch G E DePasquale N P Sun S C Mogabgab W J., and Hale A R Endocarditis in mice infected with Coxsackieviru B4 Science 151 447 1965
3 Sun S C., Colcolough H L Burch G E DePasquale N P and Sohal R S Immunofluorescent study of B4 Coxsackievirus valvulitis in mice Proc Soc Exp Biol Med 125 157 1967
4 DePasquale N P., Burch G E Sun S C., Hale A. R., and Mogabgab W J Experimental Coxsackievirus B valvulitis in cynomolgus monkeys AM HEART J 71 678 1966
5 Burch G E and DePasquale N P Viral endocarditis AM HEART J 67 ?1 1964
6 Burch G F and Colcolough H L Viral valvulitis, AM HEART J 78 119 1969
7 Sun S C Colcolough H L Sohal R S., DePasquale N P and Burch, G E Coxsackievirus valvulitis and myocarditis observed at routine autopsy Experentia 23 1041 1967
8 Blailock, Z R Rabin E R and Melnick J L Adeno virus endocarditis in mice Science 157 69 1967
9 Burch G E Harb J M Colcolough, H L and Tsui C Y Encephalomyocarditis virus infection of the new born mouse myocardium an electron microscope study Arch Intern Med 127 148 1971
10 Kilham L Mason P., and Davies J N P Host virus relations in encephalomyocarditis virus infections II Myocarditis in mongooses, Am J Trop Med Hyg 5 655 19 6
11 Pearce J M Cardiac lesions in rabbits produced by a filtrable virus (Virus III) Arch Pathol 28 8 7 1939
12 Pearce J M Susceptibility of the heart of the rabbit to specific infection in viral diseases Arch Pathol 34 319 1942
13 Case Records of the Massachusetts General Hospital 19 4 1963 N Engl J Med 268 780 1963 Cited by Conner M Henry J Benzing G and Kaplan S Varicella myocarditis Am J Dis Child 118 899 1969
14 Levison D A Guthrie W Ward C Green D M., and Robertson P G C Infective endocarditis as a part of psittacosis Lancet 2 844 1971
15 Ward C Sagar H J Cooper D., and Ward A M Insidious endocarditis caused by *Chlamydia psittaci* Br Med J 4 734 1975
16 Dick D C McGregor G A Mitchell, K G Sommer ville R G and Wheatley D J Endocarditis as a manifestation of *Chlamydia B* infection *(psittaci)* Br Heart J 39 914 1977
17 Ward C and Ward A M Acquired valvular heart disease in patients who keep pet birds Lancet 2 734 1974
18 Ward C Rheumatic heart disease psittacosis and the importance of epidemiology AM HEART J 95 266 1978
19 Wilson H G Neilson G H Galea E G., Stafford G and O'Brien M F Q fever endocarditis in Queensland Circulation 53 680 1976
20 Robson A O and Shimmin, C G L. Chronic Q fever I Clinical aspects of a patient with endocarditis Br Med J 2 980 1959
21 Sun, S C Sohal, R. S Chu K C., Colcolough H L Leiderman E., and Burch G E *Mycoplasma gallisepticum* infection in mice and cynomolgus monkeys. A histologic, immunofluorescence and electron microscopic study of the heart Am J Pathol 53 1073 1968
22 Sun S C Sohal R S Burch G E Chu K C and Colcolough, H L Coxsackievirus B pancarditis in cynomologus monkeys resembling rheumatic heart lesions Br J Exp Pathol 48 655 1967

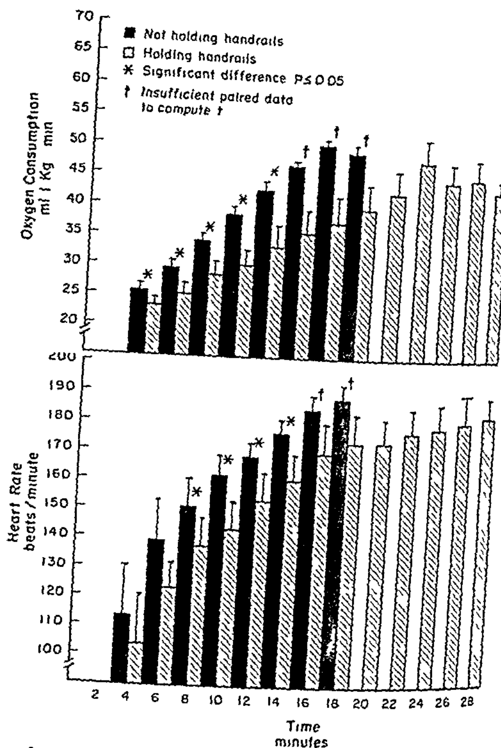


Fig 1 Oxygen consumption and heart rate responses to experimental conditions

levels A walking pr [illegible] hanging speed was used to minimize differen [illegible] al efficiency

Heart rate was m [illegible] ng standard electrocardiographic procedures wh [illegible] n [illegible] mption was measured serially with a Beckm [illegible] M [illegible] asurement Cart This system's characteristi [illegible] bed previously Calibration of the system w [illegible] and after each test Attainment of max [illegible] n [illegible] mption by each volunteer was considered a [illegible] when the criteria established by Mitchell and coll [illegible] by Issekutz and associates were met

Data were treated with non-directional [illegible] determine whether differences existed (p [illegible]

Fig 1 illustrates the oxygen cost and heart ra [illegible] each condition The differences were statis [illegible] ($p \le 0.05$) In all cases, observed values [illegible] subjects were allowed handrail assistance [illegible] oxygen consumption and heart rate values [illegible] cantly different when both conditions were compa[illegible] parison of exercise duration under both cond [illegible] strated a dramatic increase when handrail [illegible] permitted ($p \le 0.01$) Mean values for [illegible]

sorders associated with that state The concept of closed iest cardiac massage was not recognized in the 18th century it a need to do something for the cardiac situation no doubt d to the recommendation for the use of electricity Hosack fers that the rationale for the use of electricity was its then ll established and well recognized action on the muscle er It was in the 1780s that Galvani observed that by uching the nerves or the muscles with a piece of metal onnected to an electrostatic machine the muscles could be ade to contract The Humane Society of New York believed ectricity to be a most powerful agent a very proper medy" The society warns however that in all ca es the achine should be made to excite powerfully otherwise the tempt to use it will be a loss of time and so the precious oments of recovery may be lost forever A procedure was itlined by which the patient was "electrified for four or five inutes the hand of one of the attendants being applied close the body so as to take strong sparks which should be awn from the left side over the heart If that procedure did ot produce the appearance of life or motion they recom ended that light shocks (which should be increased each eration) should be sent from the breast bone through to the ick or from side to side so as to excite the heart to action if ssible This latter effort would certainly appear to be in ie with our present day concepts of closed chest cardiac imulation as demonstrated by Zoll. These early investiga ors did warn of the need for this procedure to be performed ily by experienced operators Hosack also warns that to get i electrical apparatus in readiness requires a considerable ngth of time especially on a damp day in which time the tent spark of life may be entirely destroyed On reading the ove one cannot help but wonder whether these patients on casion and quite fortuitously might have been helped by fibrillation (we are all aware of how small a shock is casionally effective in cardioversion of various arrhythmias) or periods of cardiac pacing (the repeated light shocks applied to the chest) Could the latter have been the forerunner of the external pacemaker a concept which did not become a reality for another 150 years?

How many lives were actually saved by these methods would be impossible to estimate One cannot help but be impressed by the degree of sophistication suggested by the practitioners of that period Principles and therapeutic inter ventions common to the practice of cardiopulmonary resusci tation that most would have associated with modern medical practices, were actually in vogue almost 200 years ago

Carl E Bartecchi MD FACP
Dept of Medicine
Southern Colorado Clinic
2002 Lake Ave
Pueblo Colo 81004

I am grateful for the assistance of Miss Marilyn Fransiszyn Reference and Manuscript Librarian of the Osler Library McGill University

REFERENCES

1 Editorial Near-drowning Lancet II 194 1978
2 Hosack D An enquiry into the causes of suspended animation from drowning with the means of restoring life New York 1792 Thomas and James Swords Print ers
3 Constitution of the Humane Society of the State of New York, July 12 1 94
4 Reece R The Domestic Medical Guide London 1803 C Stower Printer
5 Rubenstein E Drowning and near-drowning Scientific American Medicine II 8 IX 1 1979
6 Margotta R The Story of Medicine New York 1968 Golden Press.
7 Zoll P M Resuscitation of the heart in ventricular standstill by external electrical stimulation N Engl J Med 247 768 1952

rrors in predicting functional capacity from treadmill exercise stress test

xercise stress testing as a diagnostic procedure for ischemic eart disease has been used by qualified physicians for many ars Since physical activity has been shown to be a useful odality for improving functional capacity in cardiac itients, knowledge of the individual s aerobic level and heart ite response is essential if such prescribed activity is to be lministered safely and effectively Though direct oxygen onsumption measurements are more accurate than predicted alues, especially with cardiac patients the additional equip ent and procedural requirements make such an evaluation either practical nor economical in many clinical situations s a result nomograms, tables and formulae have been eveloped for estimation of the patient s ability to use oxygen uch estimates have been derived from exercise of a highly andardized nature It has been suggested that wide varia tions about estimated values can be expected especially if protocols used for particular nomograms or tables are not strictly followed Thorough documentation of these varia tions have not been reported The purpose of this investigation was to compare oxygen consumption values during a progres sive treadmill exercise stress test while either allowing sub jects to use handrails for enhanced stability or not allowing such assistance

Six healthy male volunteers who were classified as follow ing an active lifestyle but who were not considered to be in a trained state were used as subjects Their characteristics expressed as mean values were age = 26 6 (± 2 1) years weight = 71 5 (± 3 3) kilograms percent body fat = 12 (± 2.3) and maximum oxygen consumption = 48 1 (± 5 9) ml /kg minute In each case the subject worked to maximal

00?-8 03/80/100 81 + 03500 30/0 © 1980 The C V Mosby Co

of mitral valve leaflets which bulge than with normal leaflets The electrophysiologic basis for arrhythmias in association with the mitral valves themselves and of intrinsic mitral valve muscle fiber origin needs study

George E Burch MD
Tulane University School of Medicine
and Charity Hospital of Louisiana
New Orleans La

REFERENCES

1 Burch G E and DePasquale N P Time course of tension in papillary muscles of the heart Theoretical considerations J A M A 192 701 1965

2 Wit A L Fenoglio J J Jr Wagner B M and Bassett A L Electrophysiological properties of [illegible] muscle in the anterior mitral valve leaflet [illegible] adjacent atrium in the dog Possible implications [illegible] genesis of atrial dysrhythmias Circ Res 32 [illegible]

3 Bassett A L Fenoglio J J Jr Wit A L [illegible] R J and Gelband H Electrophysiologic and [illegible] structural characteristics of the canine tricuspid [illegible] Am J Physiol 230 1366 1976

4 Wit A L and Cranefield, P F Triggered [illegible] cardiac muscle fibers of the simian mitral valve Circ Res 38 85 1976

5 Cranefield P F Action potentials, afterpotentials and arrhythmias Circ Res. 41 415 19[illegible]

Alcohol and coronary heart disease

Several epidemiologic studies have suggested that men who consume small to moderate amounts of alcohol daily have a decreased risk of coronary heart disease (CHD) This relationship deserves careful assessment both because of the high frequency of CHD and the documented health hazards of excessive alcohol consumption

Our recent study of 568 married white men who died from CHD and an equal number of matched controls found that those drinkers who consumed two ounces or less of alcohol per day had a significantly lower risk of CHD as compared to non drinkers This finding was similar for beer wine and liquor As compared to non-drinkers, the relative risk of death from CHD for light to moderate beer drinkers was 0 3 for wine drinkers 0 3 and for liquor drinkers it was 0.2 In contrast consumption of more than two ounces of alcohol per day in the form of any of these three types of beverages was clearly not associated with any reduction in coronary deaths and may have been compatible with an increase in risk.

These results are consistent with those of three prospective cohort studies the Framingham Heart Study the Kaiser Permanente Study and the Honolulu Heart Study In the Framingham data the relative risk of myocardial infarction (MI) for consumers of more than 30 ounces of alcohol per month was 0 The data from Japanese men in Hawaii showed a linear protective effect of alcohol with a relative risk of 0 46 in those consuming more than 40 ml per day This effect was limited to current drinkers the relative risk in past drinkers was 1 3 The association in the Kaiser data was statistically significant but as presented it did not permit calculation of a relative risk estimate

On the other hand the Western Electric Study[4] did not show any relation of CHD to alcohol consumption but the amount of alcohol [illegible] specified and it is not clear that the analysis was [illegible] A positive relation of alcohol consumption to MI was noted in a small Swedish cohort study [illegible] was defined by registration with a [illegible] however the subjects denoted as con[illegible] have been heavy drinkers A recent case-control study of 4[illegible] hosp[illegible] of non fatal MI and 2 5[illegible] controls concluded [illegible] any major over all association but tended to [illegible] inverse relation with moderate alcohol consumption [illegible] protective effect was primarily noted in smokers [illegible] relative risk was 0 [illegible] as compared to non-drinkers [illegible]

The biologic basis for the effect of alcohol on CHD [illegible] uncertain but one possible mechanism may be [illegible] lipids caused by alcohol In one experimental [illegible] Swedish medical students consumed 6 g of alcohol [illegible] five week period During this time the alpha [illegible] level itself a preventive factor for MI increased [illegible] imately 30% above baseline The Cooperative Lipoprotein Phenotyping Study has found a consistent positive [illegible] between alcohol consumption and high density lipoprotein levels in various parts of the United States, with [illegible] coefficients ranging from 0 19 to 0 [illegible] This [illegible] found an inverse association between alcohol [illegible] and low density lipoprotein levels, although the [illegible] was not as strong Henze and associates have [illegible] association between the amount of wine consumed [illegible] alpha lipoprotein level in a cross-sectional study [illegible] Roman males Using a five-level categorization of [illegible] sumption the correlation with alpha lipoprotein [illegible] 0 13 Our most recent data for a group of [illegible] shows both elevated HDL levels as well as [illegible] alcohol consumption. In addition large doses of [illegible] cause alterations in platelet aggregation [illegible] platelets or regular consumption of small [illegible] amounts of alcohol are unknown but platelets [illegible] a role in the pathogenesis of MI and platelet [illegible] decrease risk of MI [illegible]

The effects of alcohol on CHD may not be [illegible] direct mechanisms, however Of special interest [illegible] tionships of alcohol and CHD to personal [illegible] and diet Much of the apparent effect of alcohol on CHD [illegible] be explained by its association with other variables [illegible]

Several studies have suggested an [illegible]

0002-8703 80 100 [illegible] 0[illegible] The C V Mosby

otocols were 15 ± 2 76 minutes and ?5 2 ± 7 16 minutes spectively

Allowing patients to grasp handrails for support during a eadmill stress test is often necessary In this study subjects ere discouraged from applying tension to their grip during ie handrail assisted condition though this factor was not iantitated

With the substantial reduction in oxygen cost and heart te at any given submaximal load when using the handrail r support one would expect to see an increase in exercise iration When one considers the importance of duration in timating oxygen cost from published tables close tention should be paid to factors altering this parameter ermitting handrail support also conflicts with the assumpons of Balke and Ware in calculating oxygen cost from eadmill speed and grade The use of heart rate as an *dicator of symptom onset and intensity when writing an* tercise prescription is also adversely affected by such a ipport type protocol

As a result of the data presented it is apparent that curate determination of those values necessary for safe and fective prescription writing is not possible unless direct ieasurement is made or unless strict adherence to specified rotocols is maintained This appears to be of major impor ince when dealing with cardiac patients In this study using oung healthy subjects the average error in prediction of V O hen duration was used as the index was 17.5% A erage eart rate values showed a 9 5% deviation Considering that iese values were in the direction of indicating a greater apacity than really existed serious attention should be paid o treadmill test protocol administration

Kerry E Ragg Ph.D
Thomas F Murray B.S
Linda M Karbonit B.S
David A Jump B.A
Work Physiology Laboratory
Dept of Zoology & Microbiology
Ohio University
Athens Ohio 45701

REFERENCES

1 Ellestad M H Stress Testing Principles and Practice 6th ed Philadelphia 19 8 F.A Davis Company p 40
2. Bruce F A Kusumi M S and Hosmer D Maximal oxygen intake and nomographic assessment of functional aerobic impairment in cardiovascular disease AM HEART J 85 546 1973
3 Hellerstein H K Hirsch, E Z., and Ader R Principles of exercise prescription for normal and cardiac subjects, *in* Naughton J P and Hellerstein H K eds Exercise Testing and Exercise Training in Coronary Heart Disease New York 1973 Academic Press pp 129 168
4 Adams G E Marlon A M and Quinn E J The disparity between predicted and measured oxygen uptake in cardiac patients during treadmill graded exercise testing (Abstract) Med Sci. Sports 11 95 Spring 1979
5 Balke B and Ware R W An experimental study of physical fitness of Air Force personnel U S Armed Forces Med J 10 675 1959
6 Astrand P O and Rodahl K Textbook of Work Physiology 2nd ed. New York 1977 McGraw Hill Book Company p 347
7 Wilmore J H Davis H A and Norton A C An automated system for assessing metabolic and respiratory function during exercise J Appl Physiol 49 619 1976
8 Mitchell J H., Sproule B J and Chapman C B Physiological meaning of the maximum oxygen intake test J Clin Invest 37 538 1958
9 Issekutz B Jr Birkhead N C and Rodahl K Use of respiratory quotients in assessment of aerobic work capacity J Appl Physiol 17 47 1962
10 Ford A B and Hellerstein H K Energy cost of the Master s two step test J A M.A 164 1868 1967

f the mitral valve and arrhythmias

: recently exaggerated and often unfounded diagnosis of lapsed mitral valve with associated arrhythmias especially tricular premature contractions stimulates thought as to iossible mechanism for the arrhythmias claimed to be ited to prolapsed mitral valve leaflets It is unlikely that tension alone which is associated with the time course of rease in intraventricular pressure during systole is respon e for even occasional premature contractions The tension :he annulus cannot be any greater than ordinary If there eally a cause and-effect relationship there must be another tor involved Any explanation at this time can only be ijectural To conjecture is permissible if the conjecture is at st thought provoking

:t is known that independent electric activity does exist in muscle fibers of the mitral valve Muscle fibers in the tricuspid valve leaflets have been shown to develop spontaneous action potentials in response to stretch and catecholamines This same type of spontaneous action potential activity has been detected in the cardiac muscle fibers of the simian mitral valve In both reports sustained rhythmic activity has also been described Wit and Cranefield have found the electric activity of the cardiac muscle fibers in the pigtail monkey to be triggerable even with the development of sustained rhythmic activity Verapamil will abolish this activity induced by catecholamines Cranefield has described characteristics of the action potential trace

Thus, it is possible that more arrhythmias may develop with disease *and/or structural changes and hydraulic* dysfunction

)? 8 03/80/100583 + 0 $00 ?0/0 © 1980 The C V Mosby Co

22 Robinette C D Hrubec Z and Fraumeni J F Chronic alcoholism and subsequent mortality in World War II veterans Am J Epidemiol 109 687 1979
23 Ferrans V J Alcoholic cardiomyopathy Am J Med Sci. 252 89 1966
24 Regan T J., Ettinger P O Haider B, Ahmed Oldewurtel H A and Lyons M M The role of ... in cardiac disease Ann Rev Med. 28 391 19..
25 Castelli, W P How many drinks a day JAMA 242 ?000 1979

Antithrombotic therapy for saphenous vein bypass grafts?

Closure of saphenous vein aortocoronary bypass grafts has been shown to occur in 19% of transplanted vessels within six months although current occlusion rates are lower Improved graft patency should increase the clinical benefits of this surgical procedure It is possible that the isolation preservation and subsequent transplantation of an autologous segment of vein into the arterial circulation leads to endothelial damage which then sets the stage for thrombotic graft occlusion due to platelet accretion and/or fibrin deposition Consequently we recently completed a randomized and controlled trial to determine whether anticoagulant or antiplatelet therapy would significantly reduce the incidence of vein graft thrombosis within six months of surgery

In this study patients undergoing bypass grafting for coronary heart disease were randomly given oral anticoagulants (warfarin sodium) antiplatelet drugs (aspirin 300 mg and dipyridamole 75 mg three times daily) or no therapy and were evaluated for graft patency by coronary angiography six months later An analysis after 50 patients were entered indicated no clinical benefit from these interventions and further that there was a greater than 90% certainty that continuing the trial would fail to improve graft patency rates in the treated groups

Why did the antithrombotic therapy fail to improve graft patency? Perhaps the selected drugs were ineffective Currently available antiplatelet agents seem to vary markedly in their pharmacology and spectrum of clinical utility For example sulfinpyrazone showed a distinct benefit in the Anturane Reinfarction Trial but had no effect in reducing mortality in Canadian patients with transient ischemic attacks Secondly starting treatment three days after surgery may have been too late if thrombosis occurred just after graft implantation Other investigators gave antiplatelet drugs prior to operation but were disheartened by excessive blood loss at surgery Third the dose of aspirin used in our trial may have been either too high or too frequent in light of the differential effects of aspirin on prostaglandin synthesis in endothelial cells and platelets Fourth technical or mechanical factors surrounding the implantation of the vein and poor blood flow in the graft due to distal coronary artery disease may be so thrombogenic that none of the currently available antithrombotic drug regimes will be effective However a recent abstract which outlined a study in whi h ulfinpyrazone was given to patients undergoing vein grafting provides a less pessimistic view Finally vein graft patency rates may have improved due to better surgical techniques so that an additional benefit of pharmacologic therapy is difficult to show For ex... patency of vein grafts to the left anterior descending coron... artery in our study was 9?%

Even though our clinical trial showed no benefit from ... antithrombotic therapy the results were still rewarding ... other information is available patients should be spared unnecessary expense and risks of bleeding from anticoagulant or antiplatelet drugs given to improve graft patency

Future studies could profitably be directed toward ... tive protocols using antiplatelet agents in clinical tr... Particularly welcome would be the development and ... tion of noninvasive techniques to assess platelet reactio... graft patency thereby sparing subjects the risks and ef... forts of repeated coronary angiography

Scott H Goodnight J ...
Division of Hematology and Medical On...
George A Pan...
Shahbudin H Rahimtoola MB FRC...
Division of Card...
Department of M...
University of Oregon Health Sciences C...
Portland Ore...

REFERENCES

1 Bonchek L. I Rahimtoola S H Chatman B ... Rosch J Anderson R P and Starr A ... occlusion Immediate and late consequences ... peutic implications Circulation 49 II-84 19?4
2 Pantley G A Goodnight S H Rahimtoola S ... Harlan B J DeMots, H Calvin L and R... Failure of antiplatelet and anticoagulant ther... improve patency of grafts after coronary by... controlled randomized study N Engl J Med 3... 1979
3 Freiman J A Chalmers T C Smith H and K... R R The importance of beta the type II er... sample size in the design and interpretation of ... randomized control trial, N Engl J Med 29... 1978
4 The Anturane Reinfarction Trial Research Gro... finpyrazone in the prevention of cardiac d... myocardial infarction The Anturane Re... N Engl J Med 298 ?90 19?8
5 The Canadian Cooperative Study Group A ... trial of aspirin and sulfinpyrazone in threatened ... N Engl J Med 299 53 19?8
6. Torosian M Michelson F L Morgan ... and Co... MacVaugh H III Aspirin and ...

000? 8?03/80/100 8? + 0? 800 ?0 0 0 1980 The C ...

.,_ A behavior pattern in men and the risk of MI One might ›eculate that some feature of this pattern makes these men ss likely to be light to moderate consumers of alcohol or lternatively that alcohol consumption may modify behavior atterns The relation of Type A behavior pattern to alcohol itake is not clear and studies of behavior patterns and CHD ave not included quantitative data on alcohol consumption ome investi ations have suggested that coronary e ent iay be preceded by an increase in the number and severity of fe changes although this association ha not been found in ll studies[20] Again it is possible that such life changes may lter alcohol consumption or themselves may be affected by ise of alcohol It is also necessary to consider alcohol as a ietary component and weigh the effects of alcohol consump-ion on the intake of other nutrients. This task is complicated oth by continuing uncertainty over the role of diet in CHD nd by the problems of measuring dietary intake in epidemio-ogic studies

Understanding of the relationship of alcohol to CHD would e substantially advanced by studies considering the variables ioted above. It would also be advantageou to have more data n the association in women In addition the possibility of nteractions between alcohol consumption and known risk actors for CHD such as cigarette smoking deserves investiga ion The benefits and disadvantages of an agent are often best letermined by a well-designed randomized treatment trial ind after careful consideration of the ethical and practical ssues, such an evaluation of alcohol consumption might well e informative

Currently when advising patients concerning alcohol the mphasis should remain on the many documented adverse ffects of excessive use of alcohol, including the risk of nyocardial disease[21] We do not think that there is evidence it this time to claim preventive or therapeutic benefit for light o moderate use of alcohol for coronary disease Caution is varranted both because our understanding of the relation of ilcohol to CHD is insufficient for the reasons noted above ind because the general problem of translatin epidemiologic bservations to therapeutic intervention applies especially to ilcohol with its complex metabolic physiologic and psycho ogic effects Even if one believes that the statistical associa ion is causal, the words of Ca telli seem well chosen with ' million alcoholics in this country we perhaps have a ssa e for which the country is not yet ready

Dent. A Evans MD
Walter C Willett MD
Charles H Hennekens MD
The Channing Laboratory
180 Longwood Ave
Boston MA 0211ɔ
and Peter Bent Brigham Ho pital Boston

r H nn kens is recipi t of Resear h Caree D l pm nt a d (N HL 00?96) from th Nation l Heart Lu g d Blood t tute

FERENCES

Kannel W B and Gordon T Some characteristics of the incidence of cardiovascular disease and death Framingham Study 16-year follow up The Framingham Study Section 26 Washington D C 1970 U S Go ern ment Printing Office
2 Klat ky A L Friedman G D and Siegelaub A B Alcohol consumption before myocardial infarction Ann Intern Med 81 294 19 4
3 Yano K., Rhoads, G G., and Kagan A. Coffee alcohol and ri k of coronary heart disease among Japanese men living in Hawaii N Engl J Med. 297 405 1977
4 Hennekens C H., Rosner B and Cole D S Daily alcohol consumption and fatal coronary heart disease Am J Epidemiol 107 196 1978
5 Hennekens C H Willett W., Rosner B Cole D S and Mayrent S L. Effects of beer wine and liquor in coronary deaths J A.M.A 242 1973 19 9
6 Paul O Lepper M H., Phelan W H., Dupertuis G W., MacMillan A., McKean, H., and Park H A longitudinal study of coronary heart disease Circulation 28 20 1963
7 Wilhelmsen, L. Wedel H., and Tibblin G Multivariate analysis of risk factors for coronary heart disease Circulation 48 950 1973
8. Stason W B., Neff R K., Miettinen O S., and Jick, H.. Alcohol consumption and non fatal myocardial infarction Am J Epidemiol 104 603 1976
9 Belfra e P Berg B Ha erstrand I Nilsson Ehle P., Tonnquist H and Wiebe T Alterations of lipid metabolism in healthy volunteers during long term ethanol ingestion, Eur J Clin Invest 7 127 1977
10 Gordon T Castelli W P., Hjortland, M C., Kannel W B and Dawber T R High density lipoprotein as a protective factor against coronary heart disease the Framingham Study Am. J Med. 62 707 1977
11 Castelli, W P Doyle J T Gordon T., Hames C G., Hjortland M., Hulley B Kagan B., and Zakel W J Al ohol and blood lipids the Cooperative Lipoprotein Phenotyping Study Lancet 2 153 1977
12. Henze K., Bucci, A., Signoretti P., Menotti, A., and Ricci, G Alcohol intake and coronary risk fa tors in a population group of Rome Nutr Metab 21(Suppl. 1) 15 1977
13 Willett W C., Hennekens C H., Siegel A J., Adner N and Castelli, W B Alcohol and blood lipids among marathon runners CVD Epidemiol. Newsl. No 28 5 February 1980
14 Haut M J., and Cowan D H. The affect of ethanol on hemostatic properties of human blood platelets, Am J Med. 56 2' 1974
15 Haerem J W Platelet aggregates and mural microthrombi in the early stages of acute fatal coronary disease Thromb Res 5 243 1974
16 The Anturane Reinfarction Trial Research Group Sulfinpyrazone in the prevention of cardiac death after myocardial infarction N Engl. J Med 298 289 1978
17 Jenkins, C D Medical progress Recent evidence supporting psychologic and social risk factors for coronary disease N En l. J Med 294 987 1033 1976.
18. Theorell, T and Rahe R. H Behavior and life satisfactions characteristics of Swedish subjects with myocardial infarction J Chronic Dis. 25 139 1972.
19 Rahe R. H., Romo, M., Bennett D., and Siltanen P Recent life changes, myocardial infarction and abrupt coronary death, Arch. Intern. Med. 133 221 1974
20 Theorell T., Lind E., and Floderus, B The relationship of disturbing life-changes and emotions to the early development of myocardial infarction and other serious illnesses Int J Epidemiol. 4 281 1975
21 Schmidt W., and Popham R. E. Heavy alcohol consumption and physical health problems A review of the epidemiologic evidence Drug and Alcohol Dependence 1 27 1975-1976.

nificantly less than the control value In spite of this the arterial blood pressure did not fall It should be noted that the left ventricular stroke work index at exercise was significantly improved compared to the control value Unlike the results following isoproterenol and hydralazine administration the patient did not demonstrate a resting tachycardia on either the initial catheterization or on follow up

Diazoxide is a direct vasodilator that produces a secondary increase in cardiac output due to a decrease in the afterload in the pulmonary circulation The increase in the cardiac output with diazoxide appears to be better than that seen with other vasodilators and may represent a direct inotropic action of the drug

In summary the value of isoproterenol and oxygen therapy is limited while phentolamine hydralazine and diazoxide show promise Diazoxide would appear to have some advantages since it is the only drug out of the three that causes a significant decrease in the resting pulmonary artery pressures in addition to the decrease in pulmonary arteriolar resistance and increase in the cardiac output Also since sudden death is an important feature of the syndrome the arrhythmogenic potential of resting tachycardia as seen with hydralazine must be considered

The initiating cause for primary pulmonary hypertension may vary in each patient and therefore the response to these various medications may differ Accordingly acute drug testing with these medications with later follow up may allow selection of the most appropriate drug in the individual patient Certainly the results in our study and those of Wang and colleagues indicate that further evaluation of diazoxide in primary pulmonary hypertension is warranted

W P Klinke MD FRCP(C) FACC
Director Coronary Care Unit
Royal Alexandra Hospital
Edmonton Alberta
T5H 3V9 Canada

REFERENCES

1 Sleeper J C Orgain E S and McIntosh H D Primary pulmonary hypertension review of clinical features and pathologic physiology with a report of pulmonary hemodynamics derived from repeated catheterization Circulation 26 1358 1962
2 Yu P N Primary pulmonary hypertension report of six cases and review of the literature Ann Intern M 49 1138 1958
3 Samet P Bernstein W H and Widrich J Intracardiac infusion of acetylcholine in primary pulmonary hypertension Am Heart J 60 433 1960
4 Nagasaka Y Akutsu H Lee Y S Fujimoto S and Chikamori J Long term favorable effect of oxygen administration on a patient with primary pulmonary hypertension Chest 74 299 1978
5 Daoud F Reeves J T and Kelly D B Isoproterenol as a potential pulmonary vasodilator in primary pulmonary hypertension Am J Cardiol 42 817 1978
6 Rao B N S Moller J H and Edwards J E Primary pulmonary hypertension in a child response to pharmacologic agents Circulation 40 583 1969
7 Shettigar U R Hultgren H N Specter M Martin R and Davies D H Primary pulmonary hypertension favorable effect of isoproterenol N Engl J Med 295 1414 1976
8 Ruskin J N and Hutter A M Primary pulmonary hypertension treated with oral phentolamine Ann Intern Med 90 772 1979
9 Rubin L J and Peter R H Oral hydralazine therapy for primary pulmonary hypertension N Engl J Med 302 69 1980
10 Wang S W S Pohl J E F Rowlands D J and Wade E G Diazoxide in treatment of primary pulmonary hypertension Br Heart J 40 572 1978
11 Klinke W P and Gilbert J A L Diazoxide in primary pulmonary hypertension N Engl J Med 302 [illegible] 1980
12 Koch Weser J Diazoxide N Engl J Med 294 [illegible] 1976

Of walking and dyspnea of congestive heart failure

The role of the veins in regulating the two cardiac pumps (right and left ventricles) and the flow of blood is frequently ignored The veins are the great reservoirs of the body s blood Much of the blood is stored in the legs When people walk the venous pumps in the legs readily force blood toward the heart and into the lungs since there are no valves in the heart to prevent the gushing blood from entering the lungs This shifted volume of blood is returned to the systemic venous circulation and [illegible] there when the function of the two pumps is well b[illegible] and synchronized But when there is left ventricular congestive heart failure this synchronization and balance of the two pumps (right and left ventricles) is lacking and the blood shifted to the lungs tends to accumulate in the lungs and cannot be shifted back into the tight systemic veins present in CHF The blood is not "stored in the systemic veins as is true normally Thus the pulmonary circulation remains over-engorged and the patient with left ventricular CHF becomes quite dyspneic not only because of failure of the left ventricular pump but also because of the pumping of blood or shifting of blood into the lungs by the venous pump in the legs upon walking or skeletal muscle contraction The blood returning from the arterial system cannot accumulate sufficiently in the tight systemic veins so characteristic of CHF

Physicians usually attribute the increase in dyspnea and development of dyspnea with walking (leg exercise) to the precipitation or worsening of left ventricular congestive heart failure as a result of the added work imposed on the heart

0002 8703/80/100588 + 0 $00 20/0 © 1980 The C V Mosby Co

leeding after coronary artery bypass graft surgery Ann itern Med 89 3.5 1978
urch J W., Stanford N., and Majerus, P W Inhibi on of platelet prostaglandin synthetase by oral aspirin Clin Invest 61 314 1978
affe E S and Weksler B B Recovery of endothelial cell prostacyclin production after inhibition by low doses of aspirin J Clin. Invest 63 532 1979
9 Baur H R Van Tassel R H., and Globel, F L. Effect of sulfinpyrazone on early graft closure rate after myocardial revascularization (Abstract) Circulation 60 11 402, 1979

atment for primary pulmonary hypertension

tact mechanism for primary pulmonary hypertension is wn. It is felt to be due to an inappropriate vasoconstric the pulmonary circulatory system Postulated mecha of the increase in the pulmonary artery pressure and nce characterizing this disorder include locally pro vasoconstricting substances as well as the possibility he disease may be of autoimmune origin The end result tter what the initiating cause is a progressive increase in nary vascular resistance with a concomitant and signif lecrease in cardiac output resulting in symptoms of poor ion and eventual right ventricular failure and sudden . Most of the patients studied have been young females nbing to the disease in an average of seven years

h this in mind various vasodilators have been tried include tolazoline acetylcholine oxygen and isopro ol[1-] However attempts to halt progress of the disease hese drugs have been unsuccessful.

asaka and colleagues reported a patient treated with n and phentolamine The use of oxygen alone did not cantly lower the pulmonary artery pressure while he awake With the addition of phenoxybenzamine the nary artery pressure did decrease while the patient was but not while he was awake However the pulmonary lar resistance decreased to one half the resting value At ly one month and eight months later the pulmonary pressure had returned to control values in spite of a nued decrease in the pulmonary vascular resi tance is no mention of any change in the cardiac output In a involving six patients with primary pulmonary hyper n Daoud and associates found that there was no icant and predictable response to oxygen therapy Therehe value of O therapy by itself is doubtful.

ravenous isoproterenol has been advocated by a number ithors.[1-] The response to acute treatment with this ration is variable with only two out of six patients ed by Daoud and co-workers[3] respondin, and with only atient with a response to sublingual isoproterenol In this nt the symptoms continued to progress and required five hospitalizations for acute intravenous therapy A nt studied by Shettigar and colleagues showed the same l favorable response but then a later progression despite nued therapy In both these studies significant resting cardia was observed Thus the variable response tachy a tachyphylaxis, and repeated use of intravenou admin tion was seen to limit the usefulness of isoproterenol.

cently there have been reports of the effectiveness of tolamine hydralazine and diazoxide[4-] in primary pulmonary hypertension Phentolamine both intravenously and orally has been used by Ruskin and Hutter[4] to treat a patient with typical primary pulmonary hypertension. In their patient intravenous and oral phentolamine both acute ly and chronically failed to significantly reduce the resting pulmonary artery pressure and only moderately decreased the pulmonary vascular resistance However their patient dem onstrated a significant and pronounced decrease in these indices with exercise and this effect was well preserved when the patient was restudied six months later In addition there was a significant increase in the cardiac output at both rest and exercise. A recent report by Rubin and Peter[4] outlined their use with hydralazine in four patients. The pulmonary vascular resistance decreased both at rest and exercise with a concomitant increase in cardiac output. However there was no significant decrease in pulmonary artery pressure at early and late follow up All patients had a significant increase in the resting heart rate at rest Thus, although hydralazine and phentolamine can decrease the pulmonary arteriolar resistance both acutely and chronically the continued high pulmonary artery pressure may result in continued strain on the right ventricle and further progression of right ventricular failure The patients in both studies improved symptomatical ly throughout the period of follow up Whether this will continue without further increase in the dosage of the medi cation remains to be seen

Diazoxide has been used by both Wang and colleagues and by us with similar results. In our study we administered intrapulmonary artery diazoxide to a young female who had both the clinical and objective findings of significant primary pulmonary hypertension. The pulmonary artery pressure fell from 63/30 (39) to 42/22 (28) with a concomitant decrease in the pulmonary arteriolar resistance from 430 dynes/sec./cm to 115 dynes/sec /cm In association with this, there was a marked increase in the resting cardiac output from 4 8 L/ minute to 10 4 L/minute There was no significant tachycardia at rest. The patient was then placed on oral diazoxide 300 mg. a day and was restudied six months later During this period and since the follow up catheterization, the patient has remained asymptomatic At restudy the pulmonary artery pressure was 41/19 (27) and increased to 55/29 (38) with exercise The pulmonary arteriolar resistance increased from 18_ dynes/sec./cm to 195 dynes/sec /cm with exercise Of significance was the fact that the cardiac output at rest remained high at 8 3 L/minute and increased significantly to 13.1 L/minute with exercise Throughout the study the systemic vascular resistance remained normal, although sig

-8703/80/100587 + 0? 00 20/0 © 1980 The C V Mosby Co

Letters to the Editor

Correlation between exercise hemodynamics and increased magnitude of P terminal force

To the Editor

We have reviewed with interest the paper by Di Bianco and associates "Left atrial overload A hemodynamic echocardiographic electrocardiographic and vectorcardiographic study" (AM HEART J 98 478 1979)

Their results are similar to those of a study we have previously published but that was apparently overlooked by them. Our results were in general agreement with theirs except that we found a significant correlation between the PTF V and the *exercise* PA wedge pressure and not the *resting* PA wedge pressure. None of our patients had acute myocardial infarction and all had chronic stable angina. If patients with acute infarction are excluded it is likely that the resting PA wedge pressure may not correlate with the PTF V

Udipi R Shettigar M D
Staff Cardiologist
Herbert N Hultgren M D
Chief Cardiology Service
VA Medical Center
3801 Miranda Ave
Palo Alto Calif 94304

REFERENCE

1 Shettigar U R Barry W H and Hultgren H N I wave analysis in ischaemic heart disease—an echocardiographic haemodynamic and angiographic assessment Br Heart J 39 894 1977

Reply

To the Editor

We would like to thank Drs Shettigar and Hultgren for bringing to our attention their published work. In patients with stable angina pectoris these authors demonstrated a correlation between the PTF V and the pulmonary artery wedge pressure during exercise but not at rest. Other findings in their study of patients with stable angina pectoris are supported by our evaluation of a broader patient group which included patients with acute myocardial infarction, primary myocardial disease and other disease entities. Both studies reveal the lack of correlation between hemodynamic measurements and echocardiographically determined left atrial size or P wave duration. However 11 of the 61 patients in our study had acute myocardial infarction and the question has been raised whether exclusion of this patient group might alter the significance of the correlation between the pulmonary capillary wedge pressure at rest and the PTF V. Review of our data reveals that 42 of 50 patients without acute myocardial infarction had ... of the pulmonary capillary wedge pressure and the PTF V as opposed to 9 of the 11 patients with acute myocardial infarction (p = NS). Pulmonary capillary wedge pressure and PTF V in patients without acute myocardial infarction (n = 50) were significantly related (r = 0.69 ± 0.035 SEM); this correlation did not differ from the over all group

The hypothesis that chronic intermittent increases in left atrial pressure result in the increased magnitude of the P terminal force in Lead V in patients with ischemic heart disease is tenable. It seems clear that the surface electrocardiogram for whatever reason reflects alterations of interatrial conduction time as was pointed out by Josephson and associates

Robert DiBianco
Assistant Chief of Cardiology
VA Medical Center
and Assistant Professor of Medicine
Georgetown University
50 Irving Street NW
Washington D C

REFERENCES

1 Shettigar U R Barry W H and Hultgren H N P wave analysis in ischemic heart disease—an echocardiographic hemodynamic and angiographic assessment Br Heart J 39 894 1977
2 DiBianco R Gottdiener J S Fletcher R D and Pipberger H V Left atrial overload A hemodynamic echocardiographic electrocardiographic and vectorcardiographic study AM HEART J 98 478 1979
3 Josephson M E Kaster J A and Morganroth J Electrocardiographic left atrial enlargement ... Electrophysiologic echocardiographic and hemodynamic correlates Am J Cardiol 39 967 1977

Function testing soon after acute myocardial infarction

To the Editor

Recently Theroux and colleagues showed function testing (low level exercise stress testing) performed before hospital discharge after acute myocardial infarction (A M I) is safe and can predict mortality in the subsequent year. These workers showed that the one year mortality rates were [illegible] in patients without changes in the ST segments and 2[illegible] in patients with depression of the ST segment (p < [illegible]). Because of the prognostic value of this test we were interested to learn how often a function test resulted in a change of management in patients recovering from an acute ischemic event

We examined 82 sequential function tests performed on male and 16 female patients of mean age 59 7 years (range [illegible] to 88 years) who achieved a mean M E T level of 3 [illegible] (range 1 7 to 11) on testing. Seventy three patients ([illegible]) were post-coronary recovering from an A M I, six (7.3%) were post-coronary artery bypass graft surgery (C A B G) and the remaining three patients (3 7%) had suffered an acute ischemic episode. The mean days of study was hospital day 13.3 (9 to 34 days), for the A M I patients hospital day 18.8 (10 to 34 days) C A B G patients and hospital day 11 0 (6 to 14 days) ischemic episode patients. No morbidity or mortality was seen

art by the exercise Both the cardiac pump and the venous mp are mutually contributing factors, but the role of the nous pumps in the legs and other systemic veins must not ignored in CHF The role of the venous pumps must be nsidered when explaining the dyspnea and other clinical anifestations of CHF associated with walking

George E Burch M D
Tulane University School of Medicine
and Charity Ho pital of Louisiana
New Orleans La

RENCES

Burch G E Léon Galindo J., and Cronvich J A New" treatment for chronic intractable congestive heart failure AM HEART J 91 735 1976

2 Burch, G E Of the venous pumps and congestive heart failure, AM HEART J 95 697 1978
3 Burch G E A Primer of Congestive Heart Failure Springfield Ill 1954 Charles C Thomas, Publisher
4 Burch G E A Primer of Venous Pressure (second printing) Springfield Ill., 19 2, Charles C Thomas Publisher
5 Burch, G E Congestive heart failure is not due to low cardiac output *per se* AM HEART J 94 269 1977

heart block Unfortunately the skin overlying the box became necrotic and the pacemaker box had to be exchanged but the electrode could not be removed and was left in situ

Nine months later the patient presented with pleuritic chest pain and screening showed that the abandoned electrode had migrated into the right ventricle and that the cut end of electrode had penetrated the free wall of the heart He developed signs of pericardial tamponade and required an emergency thoracotomy at which time free blood was found in the pericardial sac The redundant wire was removed and the patient made an excellent recovery

This case re-emphasizes the need for secure fixation of the cut end of retained electrodes

M S Perelman
M F Shiu
Dept of Cardiovascular Medicine
East Birmingham Hospital
Bordesley Green East
Birmingham B9 5ST
England

Reply

To the Editor

We appreciate the interesting comments of Drs Perel[illegible] and Shiu whose case report on cardiac tamponade due [illegible] catheter perforation of the right ventricular free wall confi[illegible] the conclusions drawn in our recently published manus[illegible] from similar experiences (AM HEART J 98 58 1979).

However we should like to point out that in our report[illegible] case on catheter embolization into the pulmonary artery the electrode wire was not retrieved via thoracotomy as erro[illegible]ously quoted by Drs Perelman and Shiu but in fact had to b[illegible] left in situ since thoracotomy was refused by the patient; h[illegible] died suddenly several days later

Gerd Rettig MD
Med Universitatsklinik und Polikli[illegible]
Innere Medizin [illegible]
D 6650 Homburg/Saar W Germ[illegible]

Table I

	No. of patients
New arrhythmia resulted in medication or change in medication	5
Chest pain resulted in change of medication	4
ST segment depression resulted in coronary angiogram	4
No new arrhythmia while on medication and therefore continued same	3
Chest pain resulted in a coronary angiogram	2
Blood pressure drop resulted in angiogram	2
Diminished exercise tolerance resulting in ordering a cardiac rehabilitation program not previously planned	2
Dizziness resulted in delay of discharge	1
Total	23/82 (28%)

The reasons for stopping the test were that the target heart rate was achieved in 41 patients (50%), symptoms of dyspnea, fatigue, and leg weakness were seen in 21 patients (26%), chest pain was found in eight patients (9.8%), ST drop greater than 1½ mm appeared in seven patients (8.5%), arrhythmia was found in three patients (3.7%), and a significant blood pressure drop was seen in two patients (2.4%).

We found that in 23 of the 82 patients (28%) the performing of a function test resulted in a change in the management of the patient by the attending physician. The reasons for a change in management by the attending physicians are shown in Table I.

Thus in addition to predicting prognosis, function testing before hospital discharge resulted in a change in patient management in 28% of our patients. Function testing also allows an objective evaluation of a patient's response to low level exercise that he will experience in his home environment and allows the physician to more accurately determine the type of activities permissible for the patient at home. It also seems possible that in the future function testing may play an important role in determining which patients should have coronary angiography prior to discharge.

John K. Vyden, M.B.
Harvey L. Alpern, M.D.
Masakuni Kanagawa, M.D.
Elaine Mickle, R.N.
Harold B. Rose, Sc.D.
Cardiac Rehabilitation Service
Division of Cardiology
Cedars-Sinai Medical Center
8700 Beverly Blvd.
Los Angeles, Calif. 90048

REFERENCE

1. Theroux P, Waters D D, Halphen C, Debaisieux J C, and Mizgaza H F: Prognostic value of exercise testing soon after myocardial infarction. N Engl J Med 301:341, 1979.

Of bibliographies and medical librarians

To The Editor:

This letter is written in response to the Annotation entitled "Of bibliographies" (AM HEART J 99:401, 1980). The point made by Dr. George F. Burch that authors do not always research their topic adequately is well taken. As the editor of AMERICAN HEART JOURNAL, Dr. Burch is obviously in a position to observe the quality of literature research done by his colleagues. It is also true that a "careful review of the medical literature on any subject is an ordeal which is difficult and time-consuming." Our role as medical librarians is to aid those authors who do not have the time to do extensive research. If a physician feels that the Medline search is not adequate or preferred, most librarians will be happy to do a manual search and/or provide instruction so that the experience can be "informative, educational, and proper," as Dr. Burch suggests. Medical schools which include a segment on library/research orientations in their curricula are to be applauded for giving the student an appreciation of the literature.

Dr. Burch is incorrect, however, in thinking that Medline "retrieves publications of only the past 5 years or so"—the Medline data base includes citations from 1966 to the present.

Barbara Bury, A.M.L.S.
Daniel Jones, M.Ln.
Library
University of Texas Health Science Center at San Antonio
7703 Floyd Curl Dr.
San Antonio, Texas 78284

Reply

To the Editor:

We thank Ms. Bury and Mr. Jones for their letter. On checking with our librarian, we were informed that Medline has two types of services. The "current" Medline extends back three years, but service may be obtained as far back as 1966. It must be remembered, however, that many important contributions have been made prior to 1966. Unfortunately, a review of the literature beyond 1966 is very time consuming.

George E. Burch, M.D.
Editor, AMERICAN HEART JOURNAL
Tulane University School of Medicine
1430 Tulane Ave.
New Orleans, La. 70112

Migration of redundant pacing electrode

To the Editor:

Retting and associates recently described a case of migration of a redundant transvenous pacing electrode (AM HEART J 98:587, 1979). In their case the electrode settled in the pulmonary artery and was retrieved via a thoracotomy.

We have had a similar experience but with a more serious consequence. The patient, a 74-year-old man, required permanent pacing because of Stokes-Adams attacks due to complete

Association for Advancement of Behavior Therapy

The 14th annual convention of the Association for Advancement of Behavior Therapy will be held on November 20 through 23 1980 at the New York Hilton New York City Included will be five sections of the 8 hour basic course in Clinical Behavior Therapy 12 pre convention institutes lasting 5 hours and limited to 30 participants and 40 workshops lasting 3 hours and limited to 125 attendees In addition there will be symposia panel discussions invited addresses and poster board sessions all presented by experienced professionals in the field

For further information regarding this convention contact Steven C Hayes Ph D Program Chairperson Association for the Advancement of Behavior Therapy 420 Lexington Ave New York N Y 10170 Telephone (212) 682 0065

Europacing 81

The Second European Symposium on Cardiac Pacing will be held in Florence Italy on May 4th through 6 1981 The symposium is organized by the European Working Group on Cardiac Pacing in cooperation with the Italian Pacing Association Professor G A Feruglio is chairman of the organizing committee For further information regarding this symposium contact The Secretariat Europacing 81 O I C Organizzazioni Congressi Via G Modena 19 50121 Firenze (Florence) Italy

Third World Congress on Pain

The Third World Congress on Pain sponsored by the International Association for the Study of Pain will be held on September 4 through 11 1981 in Edinburgh Scotland For further information contact Third World Congress on Pain University of Edinburgh Centre for Industrial Consultancy and Liaison 16 George Sq Edinburgh, EH9 9LD Scotland, United Kingdom or Louisa F Jones B S Executive Secretary International Association for the Study of Pain Dept of Anesthesiology RN 10 University of Washington, Seattle Wash 98195

Workshops in Interventional Radiology

The Division of Cardiovascular Radiology Department of Radiology Johns Hopkins University School of Medicine will sponsor a series of one day workshops in interventional radiology Intensive teaching to small groups will be provided in vascular embolization procedures percutaneous biliary drainage and transluminal angioplasty Workshops will be conducted on Saturday December 6 1980 and on Saturday February 7 1981 The number of course participants is limited to 20 Workshops are approved for 4 hours of Category I credit For information and application forms please contact Klemens H Barth M D Director Interventional Radiology Workshop The Johns Hopkins Hospital Baltimore Md 21205 Telephone (301) 955 6348

Book reviews

Interpreting the Electrocardiogram By James S Fleming New York 19 9 Update Publishing International Inc 13 pages.

This is an atlas type book designed to teach physicians how to interpret electrocardiograms The technic used is to teach the student how to interpret patterns i e by memorizing patterns without much knowledge of the fundamental of electrocardiography The fundamental aspects of electrocardiology and electrophysiology are not discussed The book is presented in such a manner that the reader need not have a knowledge of membrane potentials or the electric activation of the myocardium or the phenomenon of recession This book should prove useful to nurses and paramedical personnel who wish to have a practical knowledge of the patterns of electrocardiography The diagrams are many and simple and the tracings are well chosen

Cardiovascular Physiology III Volume 18 Edited by A C Guyton and D B Young Baltimore 19 9 University Park Press 368 pages Price $34.95

This is another excellent issue of *International Review of Physiology* which is concerned with cardiovascular physiology The contributors have condensed for the reader the new things of interest in the field of cardiovascular physiology The selected eight sections include contraction and relaxation of the myocardium determinants of systemic blood flow reflex control of vascular capacitance and skeletal muscle circulation transcapillary transport of small solutes and water interstitial lymphatic flow system pulmonary transcapillary exchange and pulmonary edema and cardiogenic hypertension The more recent publications of data are well oriented with physiologic studies repeated in the more remote past Anyone involved in cardiovascular physiology and training and teaching of clinical cardiovascular problems will find this publication to be a stimulating and thought provoking source of important material This review is quite different from most annual reviews in any field of medicine in that the reports are presented as an organized review of the respective subjects The editors and contributors have produced a valuable publication

Coronary Heart Disease Third International Symposium Frankfurt Edited by Martin Kaltenbach M D Paul Lichtlen M D Raphael Balcon M D and Wolf Dirk Bussman M D Acton Mass 1978 PSG Publishing Company 346 pages Price $47 00

This report on coronary heart disease includes the presentation and discussion at the Third International Symposium held in Frankfurt during February 19 8 The many short papers are divided into eight parts Part 1 related to coronary collaterals is of particular interest not only to physiologists and anatomists but to clinicians as well The importance of the collateral circulation in ischemic heart disease is nicely presented. Part 5 is devoted to discussion of coronary spasm a subject known to be important in cardiology for many years, but of considerable interest in clinical research at present The clinical importance of coronary spasm is well discussed by investigators directly interested in the problem Part 7 is devoted to the mechanical treatment of ischemic disease This part should interest all physicians who treat ischemic heart disease The entire publication is of considerable interest and value This book is highly recommended It is easy to read the illustrations and tables are good and the discussions are of interest to anyone who manages patients with coronary artery disease This is an excellent book that can best be appreciated by critical reading and study

Ambulatory Electrocardiography By Edward K Chung New York 19 9 Springer Verlag 241 pages Price $24 90

This book is intended for training in the use of Holter monitoring in the management of cardiac disease Chung has briefly outlined the indications, applications in diagnosis, interpretation record or protocol keeping by the patient and clinical problems for which it is most useful These discussions are followed by 100 case histories and segments of recordings with interpretations The book is primarily an atlas for beginners to learn how to employ Holter monitoring in the practice of cardiology This is a good book with its primary purpose achieved The reader who is not acquainted with this procedure will find the 100 case examples interesting and challenging even to cardiologists It is not possible to critically review each case presented This must be left to the readers Nevertheless Case 36 page 8 of a supraventricular tachycardia has two questions presented by the author to his readers One is "What is the treatment of choice?" How can this question be answered without the entire clincial data Cases like this do challenge a thoughtful critical reader This is a good book which should interest beginners as a supplement to other literature on cardiac arrhythmias

Myocardial Infarction second edition By Ary Louis Goldberger St Louis 1979 The C V Mosby Company 2? pages. Price $26 50

The second edition attests to the success of the first edition. The author has added new information to assist the clinician in continuing his training in electrocardiography with emphasis on the ECG diagnostic manifestations of myocardial infarction The author is the son of Dr Emanuel Goldberger who introduced the augmented limb leads to clinical electrocardiography The book is divided into two parts part one is concerned with depolarization (Q wave) pattern simulating myocardial infarction and part two is concerned with repolarization (ST T) patterns simulating myocardial infarction It is a good book which clearly presents the problems in differential diagnosis of myocardial infarction by ECG Physicians in training will find a critical study of this book to be a valuable effort The ECG remains of paramount importance in clinical cardiology Goldberger has selected good illustrations and included a good bibliography of 6 4 well selected references Myocardial infarction is an important and common problem in the practice of medicine and the ECG is of routine use in diagnosis and management This is a good addition to the medical literature

leisure to pursue full time academic and scholarly activities Scholarship has lessened because clinical duties are too time consuming and demanding Teaching suffers and the fundamentals of medical science and the depth of critical discussions self criticism and self evaluation are at a minimum In spite of large clinics and large hospitals and capable physicians outside the schools the medical schools are in private practice and in competition with the private practitioners and private clinics bearing the burden of large budgetary problems and ever demanding large salaries of the clinical faculty and private patient care This should not be

Thus with critical review it becomes evident that we have reverted back to 1910 in medical education How did this happen? Is it good? Where are the certifying groups who review full time medical schools? Why isn t medical education being critically reviewed in 1980 with scholarship and teaching and research being made the premium for dedicated scholars and scientists in medical schools people with missionary dedication to scholarly pursuits?

Outstanding teaching and training of physicians can be done only with strictly full time clinical faculty dedicated to scholarship teaching and research—a faculty willing to accept a financial sacrifice in exchange for opportunities to study think teach and do research on a full time basis without an excessive burden of primary patient service responsibilities Sufficient people exist in medicine to provide such a faculty for all medical schools of America In 1910 a change to full time faculty developed with success This can also occur in 1980 if the various administrations in the U S and the American people wish and are willing to bear the financial burden involved

Many more medical schools with small classes and highly motivated truly full time faculties must be the objective of medical education in America for the immediate future We need at least 300 more medical schools with small st de bodies and with excellent teachers in which t objective is to provide the best medicine for t people of America and in which earning mone not paramount The scholars of medical scho students and faculty should be expected to spe money and must not be concerned with earn money They must be concerned with trainin administering to the sick emphasizing preven medicine regardless of economic or social sta of the patients The people of America will be t winner in the end and therefore the people mu provide the support without restrictions—but, n by direct or indirect payment for services (fee f service) to a so called full time clinical facult The American people will benefit from th support through the improved services of bet trained graduates who eventually enter priva practice and become the full time private ph sicians of the people It takes time to teach and advance knowledge and it takes time to practi good medicine and care for the sick When the two types of medical endeavors are attemp simultaneously by the same people both usual suffer from poor performance and certainly suf from inadequate time for thought scholarsh teaching and learning

Let us re-emerge in 1980 as we emerged in 19 with true and strictly full time clinical facult and medical schools of scholars—faculties a students interested only in learning studen thinking and venture research Let the phy cians in private practice care for the sick on fee for service basis A volunteer faculty sho exist but a strictly full time faculty dedicated t scholarship teaching and research should consti tute the core of the medical schools

REFERENCE

1 Flexner A Medical education in the United States an Canada A report to the Carnegie Foundation for the Advancement of Teaching Bull No 4 Boston, 1910 The Merrymount Press

American Heart Journal

November 1980 Volume 100 Number 5

Editorials

Of 1910

George E Burch M D
New Orleans La

The Flexner report[1] appeared in 1910 marking the beginning of significant improvement in medical education in the U S A In 1910 there were many poor medical schools in which earning money was an important objective of the clinicians who owned the schools and controlled the hospitals Preclinical faculty was hired by these clinicians The faculties were not considered full time since they practiced private medicine to earn money for themselves Scholarship science and research and investigation into the unknown were essentially non existent Students who paid their tuition were essentially assured a diploma The Flexner committee exposed the inadequate medical education and recommended drastic changes especially the need for full time clinical faculty that would be concerned with teaching research and scholarship and not with the private practice of medicine In fact the full time faculty was definitely not to practice medicine privately The faculty was to teach good medicine and to search into the unknown through research thought and discourse for the sake of advancing knowledge The strictly full time clinical faculty was to produce outstanding physicians to render care of the sick with concern for the sick according to performance background and model established by the full time clinical teachers dedicated to scholarship The full time clinical faculties were rapidly instituted after the Flexner report was published The medical schools displayed pride and extreme satisfaction with their full time clinical faculty and their accomplishments The level of academic performance and rating of each medical school were determined by size and quality of the strictly full time faculty with reward for the best clinical scholars Any clinical faculty appointee with patient service responsibility and fee for service no matter how arranged was considered a part time and not a full time faculty member Even geographic full time appointment was not permitted at the outset Those who were interested in private practice joined the part time clinical faculty and made important contributions to their respective medical schools

We are now in 1980 but back to the level of 1910 in medical education We have been there for several years a transition which started 20 or more years ago The earning of money is now a strong motivation and an overly emphasized objective and concern of teaching medical institutions At present the universities and medical centers own the faculty the hospitals and the clinics The size of the hospital number of patients and funds earned seem to reflect important qualities of achievement—the same qualities which are considered a great achievement in private non academic clinics Budgets must be met and the magnitude of salaries is the index of success and faculty satisfaction The clinical faculties are now busy practicing medicine to earn money for the medical schools so the schools can meet these budgets and pay salaries including their own The faculties no longer are free and at

From the Department of Medicine Tulane University School of Medicine New Orleans, La.

Received for publication Dec 6 1979

Reprint requests George E Burch M D 1430 Tulane Ave., New Orleans, La. 0112

the epicardial and body surface ECG could be demonstrated which invalidated the earlier conclusions Durrer and associates[9] reported that even an SEI of extremely small size (1 cm in diameter) can lead to abnormal Q waves The 1957 report from Prinzmetal's laboratory and Durrer's studies are in full agreement with practically all later autopsy reports on the ECG in SEI Abnormal Q waves can be found in most SEI and TMI cases but they may be absent in a substantial number of infarcts of both types

Scher[1] has been one of the few investigators who took notice of the changing concepts in Prinzmetal's laboratory In his excellent review on the Excitation of the Heart in 1962 he stated The work of Prinzmetal and his colleagues deserves some comment All of the early papers in a very large series stressed the fact that most of the inner layers of the wall were silent and were depolarized before the beginning of the peripheral electrocardiogram A final paper in the series re-examined the major claim (excitation of inner layers before the beginning of QRS) and found it to be incorrect It appears truly amazing that in the relatively short interval of three years between the first and second report from Prinzmetal's laboratory an erroneous concept could become so deeply ingrained in cardiologists thinking

At this point in time one is tempted to conclude that no matter how many additional autopsy studies refuting the concept of the silent SEI will be published in the next decades the public at large will probably take little or no notice We have no ready explanation for the persistence of this concept which could have been abandoned in the late fifties It may be related to the shifting emphasis toward many other investigative procedures such as coronary angiography ventriculography and others and away from postmortem studies which used to be and still remain the most essential objective evidence for the presence or absence of infarction The fact remains that both TMI and SEI can be found in substantial numbers without typical Q wave abnormalities The electrocardiogram alone seems to be of little help in the differentiation between these two types of infarct

Many reasons have been given for the absence of Q wave abnormalities in certain patients with MI The presence of multiple infarcts MI location in certain regions of the left ventricle which are relatively silent [11] and changes lim the middle or late part of the QRS are o explanations which have been offered detailed discussion goes beyond the scope o editorial

Differentiation between TMI and SEI only of academic interest because it was fe some investigators that there might be a d ence in the clinical course and prognos patients having SEI or TMI Cases with SEI believed to have a more benign course Com sons were made, therefore between th patients with QRS abnormalities and others ST T changes only [13, 14] No autopsy confirm on infarct size and extension within the ventricular wall was available From the ea discussion it should have become clear that th patients could have had TMI or SEI To ou surprise no significant differences in the clin course and prognosis could be found

It is not inconceivable that patients subendocardial lesions might have a better p nosis than those with TMI With present ele cardiographic techniques a differentiation tween SEI and TMI does not appear feas However in addition to the relative loca within the left ventricular wall for prognosis has also to consider the total muscle mass wh has become necrotic Many subendocar infarcts are very large and almost circula ring like and the total amount of dead tissue these cases is substantial [15] More detailed corre tions between enzyme levels and ECG ch might lead to better clues for estimating infa size

REFERENCES

1 Savage R M., Wagner G S Ideker R E Pod ... A., and Hackel, D B Correlation of postmortem a tomic findings with electrocardiographic chan patients with typical anterior and posterior ... Circulation 55 279 1977

2 Sullivan W Vlodaver Z., Tuna, N Long L, ... Edwards J E Correlation of electrocardiogra ... pathologic findings in healed myocardial infarction ... J Cardiol 42 724 1978

3 Raunio H Rissanen V., Romppanen T Jokinen ... Rehnberg, S Helin M., and Pyorala, K Changes ... QRS complex and ST segment in transmural and sub docardial myocardial infarctions. Am Heart J 98 ... 1979

4 Abbott J A and Scheinman M M Nondiagnostic electrocardiogram in patients with acute myocardial infarction. Clinical and anatomic correlations Am J Med. 55 608 1973

5 Wilson F N., Johnston F D Hill, I G and Gre ... C The electrocardiogram in the later stages of exp...

"Silent" subendocardial infarcts fact or fiction?

Hubert V Pipberger M D
Emigdio A Lopez M D
Washington D C

During the last 25 years it has become customary to make a distinction between electrocardiograms which are considered compatible with subendocardial infarcts (SEI) and transmural infarcts (TMI) The former are believed to lead only to ST and T wave changes whereas QRS changes and more specifically the development of abnormal Q waves are considered characteristic for TMI According to this concept the subendocardium is electrocardiographically silent as far as the QRS complex is concerned

The vast majority of autopsy correlations reported in the literature are in disagreement with this simplistic concept In most recent years Savage and associates Sullivan and colleagues and Raunio and co workers reported in great detail on a total of 154 autopsies and their ECG findings prior to the patients death There appears to be general agreement between these investigators that the majority of cases with SEI exhibit typical QRS changes and furthermore that in a substantial number of patients with TMI the characteristic Q wave changes cannot be found Raunio and co workers[3] reported only very recently in the August 1979 issue of THIS JOURNAL on a new series of 80 autopsies In this very carefully executed study 53% of the SEI cases showed QRS changes which were typical for myocardial infarct (MI) Similar QRS changes were present in 65% of the TMI patients a difference which is hardly significant

Savage and associates[1] found 11 SEI cases in their autopsy series of 24 Ten out of these or 91% could be diagnosed as infarct on the basis of typical QRS changes and only one case with a posterior SEI had no abnormal Q waves in Leads II III or a V_F Abbott and Scheinman reported on 230 patients with acute MI In 78 or 34% of these cases the electrocardiogram did not show signs which are considered diagnostic for MI Eight cases of the latter group came to autopsy and all of them were found to have TMI

The literature on ECG findings in autopsy proven SEI and TMI cases has been reviewed recently very extensively by Savage and colleagues[1] and by Raunio and co workers[3] The history goes back to Wilson and associates who described typical Q wave changes with SEI both in animals and in men[4] There appears to be overwhelming evidence that most SEI cases show Q wave abnormalities which are typical for MI Furthermore the percentage of SEI cases which do not exhibit characteristic Q wave changes appears to be very similar to that of TMI cases without Q wave abnormalities To distinguish between SEI and TMI on the basis of the electrocardiogram seems therefore not possible

How then did the ECG differentiation between these two types of infarcts develop? The work which is most often quoted is that of Prinzmetal and associates[5] who reported in 1954 on experiments in seven dogs with chronic SEI and on twelve dogs with acute SEI From their results they concluded that subendocardial depolarization is silent and thus should not affect the electrocardiogram In a later study from Prinzmetal's laboratory in 1957 when more refined recording techniques had become available a significant contribution of the subendocardium to

From the Veterans Administration Medical Center and the Departments of Clinical Engineering and of Medicine George Washington University Washington D C

Received for publication Dec. 28, 1979

Reprint requests Hubert V Pipberger M D VA Hospital VA Research Center for Cardiovascular Data Processing, 50 Irving St NW Washington, D C 20422

0002-8703/80 110597 + 03$00.30/0 © 1980 The C V Mosby Co

Evaluation of contractile state of the left ventricle from the peak of the first derivative of the apexcardiogram

Nikolai S Kolev, M D
Varna Bulgaria

Johnston and Overy[1] were the first to report that the magnitude of the first derivative of the apex cardiogram (dA/dt) was in close relation to the contractile state of the myocardium Some authors [*] using suitable mechanical calibrating devices determined left ventricular wall velocity and other quantitative indexes from the height of dA/dt Because of the difference among individual subjects in cardiac size and body build, quantitation of left ventricular wall velocity has not been feasible by this method [7, 8]

Reale proposed an alternative approach of using the first derivative of the apexcardiogram He established the similarity between the interval from the onset of ventricular depolarization and the peak of the first derivative of the apexcardiogram on one hand and the interval from the R wave of the electrocardiogram to the peak dP/dt, on the other hand as suggested by Mason and colleagues [1]

In order to maintain the informative value of the height of the peak dA/dt and avoid the calibrating difficulties we proposed a new way of interpreting the peak dA/dt The amplitude of the peak dA/dt was expressed as a percent of the total deflection of the first derivative of the apexcardiogram

The present study was designed to assess the clinical value of measuring the peak of the first derivative of the apexcardiogram (1) by defining the normal values of the ratio of peak dA/dt a[illegible] the duration of the interval from ventric[illegible] depolarization to peak dA/dt (R to peak dA dt) (2) by investigating the effect of different pha[illegible] macologically induced variations in the contra[illegible] tile state of the human myocardium on the abo[illegible] parameters and (3) by comparing patients w[illegible] impaired left ventricular function with contro[illegible]

Subjects and methods

A left apexcardiogram and its first deri[illegible] were obtained in 104 individuals—50 normal su[illegible] jects ranging in age from 20 to 61 years (mean a[illegible] 38 ± 14 years) and 38 patients with ischem[illegible] heart disease ranging in age from 35 to 73 ye[illegible] (mean age 51 ± 16 years) In 16 additional su[illegible] jects the effect of pharmacological agents w[illegible] positive and negative inotropic action was st[illegible] ied

In the group of normal subjects no presen[illegible] history of heart disease was presented and [illegible] complete physical examination 12 lead electro[illegible] cardiogram, carotid pulse tracing apexcard[illegible] gram and chest x ray were normal

The patients with ischemic heart disease had [illegible] history of old myocardial infarction—6 month[illegible] 12 years after onset Their diagnosis was based [illegible] typical anamnestic data, electrocardiograph[illegible] examinations and increased enzyme activ[illegible] the acute phase When investigations were pe[illegible] formed all patients suffered from decompensated coronary artery disease (degree of decompensa[illegible] tion Class I to II according to the criteria of the New York Heart Association) Not included [illegible] the study were the patients on digitalis [illegible] antiarrhythmic agents and patients with bu[illegible] block

From th Medical A demy Higher Med cal Institute Department of Internal Medicine Varna Bulgaria

Received f r publicat on Feb 20 19"9

Accepted for publi ation Apr 1 19 9

Reprint requests Nikola S Kole M D Medical Ac demy Higher Medical Inst tute Dept f Internal Medicine Varna Bulgaria

0002 8"03/80/110600 + 0..00 .0 0 © 1980 The C V Mosby Co

mental myocardial infarction Trans Assoc Am Physicians 48 154 1933
6 Wilson F N Johnston F D Rosenbaum F F Erlanger H Kossmann C E Hecht H Cotrim N Menezes de Oliveira R Scarsi R and Barker P S The precordial electrocardiogram AM HEART J 27 19 1944
7 Prinzmetal M Shaw C McK Jr Maxwell M H Flamm E J Goldman A Kimura N Rakita L Borduas, J L Rothman S and Kennamer R Studies on the mechanism of ventricular activity VI The depolarization complex in pure subendocardial infarction role of the subendocardial region in the normal electrocardiogram Am J Med 16 469 1954
8 Pipberger H Schwartz L Massumi, R A Weiner S M and Prinzmetal M Studies on the mechanism of ventricular activity XXI The orgin of the depolarization complex with clinical applications AM HEART J 54 511 1957
9 Durrer D Van Lier A A W and Buller J Epicardial and intramural excitation in chronic myocardial infarction AM HEART J 68 765 1964
10 Scher A M Excitation of the Heart in Handbook of Physiology Section 2 Circulation Vol I editor W F Hamilton Washington D C 1962 American Physiological Society p 304
11 Horan L G Flowers N C., and Johnson J C Significance of the diagnostic Q wave of myocardial infarction Circulation 43 428 1971
12 Pipberger H V and Stallmann F W Computation of differential diagnosis in electrocardiography Ann N Y Acad Sci. 115 1115 1964
13 Madias J E Chahine R A Gorlin R and Blacklow D J A comparison of transmural and nontransmural acute myocardial infarction Circulation 49 489 1974
14 Rigo P Murray M Taylor D R Weisfeldt M L Strauss H W and Pitt B Hemodynamic and prognostic findings in patients with transmural and nontransmural infarction Circulation 51 1064 1975
15 Cook R W Edwards, J E., and Pruitt R D Electrocardiographic changes in acute subendocardial infarction I Large subendocardial and large transmural infarcts Circulation 18 603 1958

Copyright information

The appearance of a code at the bottom of the first page of an original article in this journal indicates the copyright owner s consent that copies of the article may be made for personal or internal use or for the personal or internal use of specific clients This consent is given on the condition however that the copier pay the stated per copy fee through the Copyright Clearance Center Inc 21 Congress Street Salem Mass 01970 617 744 3350 for copying beyond that permitted by Sections 107 or 108 of the U S Copyright Law This consent does not extend to other kinds of copying such as copying for general distribution for advertising or promotional purposes for creating new collective works or for resale For reprint quantities of 50 or more contact Publisher

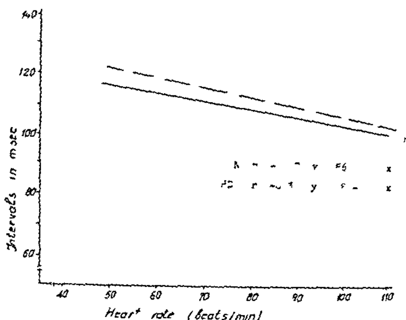


Fig 2 Linear regression analysis between interval R to peak dA/dt and resting heart rate in normal subjects (N) and in patients with ischemic heart disease (IHD)

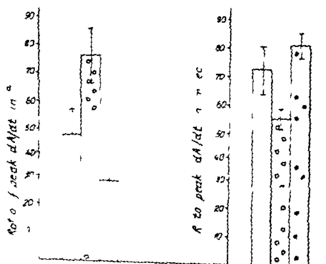


Fig 3 Mean changes in the average values of ratio of peak to total amplitude (dA dt) (left) and interval R to peak dA/dt (right) at rest (plain bar) after beta adrenergic stimulation (bar with open circles) and after beta adrenergic blockade (bar with solid circles) Each bar represents the mean ± SD

−29 ± 15 (p < 0 001) and the interval R to peak dA/dt was increased by 9 ± 6 msec (p < 0 02) (Figs 3 and 4)

In the patients with ischemic heart disease a decrease of the ratio of the peak dA/dt occurred and its mean value amounted to 32 ± 13% (p < 0 001) In the same patients an elongation of the interval R to peak dA/dt with a mean value 121 ± 15 msec (p < 0 01) was also found

Discussion

Although the exact genesis of the apexcardiogram is not clearly understood many observations indicate that the configuration the time course the height and the slope (especially in the isometric phase) of the apexcardiogram are significantly correlated with left ventricular pressure[3,4] Reale[7] reported the similarity in time and contour between the first derivative of the left ventricular pressure and the first derivative of the apexcardiogram It was shown in experimental studies[3,4] and clinically[5] that correlation between the first derivative of the apexcardiogram and left ventricular pressure during hemodynamic changes was fairly good All the authors used a calibrating device when determining the height of the first derivative of the apexcardiogram and expressed its value in different units—mm Hg/sec[3,4] X/sec[5] or g/sec[6]

Quantitation of peak dA/dt by use of the absolute value of amplitude have been [illegible] because of differences among individual subjects in cardiac size and thoracic shape[3,4] Owing to the difficulties in calibrating the sensing device and therefore in assessing units of measurement of the first derivative of the apexcardiogram we examined the relative height of the peak of dA/dt as percent of the total amplitude of the first derivative

Our data for parallel modifications of the ratio of peak dA/dt after pharmacologically and [illegible]

Pharmacological interventions were performed in 16 volunteers in order to study the effect of positive and negative inotropic drugs on the first derivative of the apexcardiogram Isoprenaline infused intravenously at a rate of 0 003 μg/kg/minute and propranolol (Obsidan GDR) 5 mg intravenously were given in order to obtain the appropriate effect Informed consent was obtained from the subjects prior to the examination

The polygraphic tracing was performed by rotating recumbent subjects 30 to 50 degrees toward the left lateral decubitus position Apex cardiograms were recorded by means of a piezo electric transducer (RFT GDR) with an infinite time constant The transducer was held by a circumferential adhesive strap at the point of *maximal impulse of the apex beat of the heart*

The first derivative of the apexcardiogram was obtained by passing the pulse wave of the apex cardiogram through a resistance capacitance (RC) network differentiator The differentiator was constructed in our laboratory and consists of a low pass filter followed by a high pass filter both filters having the same time constant (0 1 msec) with a flat response in a range of 0 to 80 Hz The attenuation of the differentiator is down 20 db per decade Thus high frequencies are accentuated and low frequencies are attenuated

During mild expiratory apnea simultaneous records were made of the electrocardiogram phonocardiogram apexcardiogram and dA/dt on a six channel recorder (6 NEK 3 GDR) Paper speed was 100 mm/sec

Analysis of the simultaneous tracings (Fig 1)

1 Ratio of positive amplitude to total amplitude of the first derivative of the apexcardiogram expressed as a percent of total deflection

2 Interval from R of the electrocardiogram to the peak of the first derivative of the apexcardiogram (R to peak dA/dt) This interval was corrected for heart rate by formulas from regression analysis in Fig 2 which represents the relation between heart rate and survival R to peak dA/dt in normals and in patients with ischemic heart disease

Results

In the control group the mean ratio of the height of the peak dA/dt was 48 ± 14% of the total deflection of the first derivative of the apexcardiogram The interval from R of the electrocardiogram to the peak of the dA/dt was 73 ± 15 msec

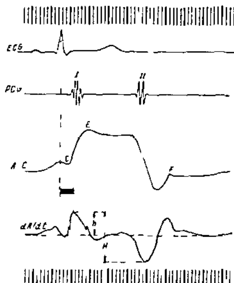


Fig 1 Simultaneous recordings of electrocardiogram *(ECG)* phonocardiogram *(PCG)* apexcardiogram *(ACG)* and first derivative of apexcardiogram *(dA/dt)* *Blackened area* denotes the interval from R wave of ECG to peak dA/dt *h* denotes the peak amplitude of dA/dt and *H* represents the total amplitude of dA/dt *The vertical lines* determined 0 02 sec intervals

To evaluate the possible influence of resting heart rate on interval R to peak dA/dt a linear regression analysis of the first variable with the latter was carried out in the 56 normal subjects and in 38 patients with ischemic heart disease There was some tendency of interval R to peak dA/dt to decrease at increasing resting heart rate (Fig 2) however the inverse correlation was very slight although significant (normal subjects $r = -0\ 37$ $p < 0\ 01$ ischemic heart disease $r = -0\ 39$ $p < 0\ 01$)

Sixteen young adult men with no cardiac disease submitted to intravenous injection of isoprenaline The ratio of peak to total amplitude (dA/dt) showed augmentation and its mean value amounted to 81 ± 16% whereas the mean basal value was 49 ± 15% ($p < 0\ 001$) moreover the interval R to peak dA/dt was reduced by −16 ± 5 msec ($p < 0\ 001$) *In the same subgroup a deter*mination repeated after the infusion was stopped showed parallel returns of the above parameters toward perfusion levels Following beta adrenergic blockade with propranolol the mean ratio of peak to total amplitude was diminished to

Summary

Simultaneous records of the electrocardiogram, phonocardiogram apexcardiogram (ACG), and the first derivative of the apexcardiogram (dA/dt) were obtained in 50 normal subjects and in 38 patients with ischemic heart disease This allowed us to measure the ratio of peak dA/dt to total amplitude of the first derivative in percent and the interval from electrical stimulation to peak dA/dt (R to peak dA/dt) In 16 additional normal subjects the effects of pharmacological agents with positive and negative inotropic action were studied with the above parameters During isoprenaline infusion the ratio of peak to total amplitude dA/dt was increased and the interval R to peak dA/dt was shortened, while after propranolol the ratio of peak dA/dt diminished and the interval R to peak dA/dt showed elongation

In normal subjects the ratio of peak dA/dt averaged 48 ± 14% and it is significantly lower in patients with ischemic heart disease (32 ± 13%, $p < 0.001$) In controls the interval R to peak dA/dt was 73 ± 15 msec whereas in ischemic heart disease it showed elongation (121 ± 15 msec $p < 0.01$)

It is concluded that the ratio peak dA/dt and the interval R to peak dA/dt expressing noninvasively the rate of pressure changes and the duration of the development of maximum tension during isovolumic contraction provide useful information on left ventricular function

REFERENCES

1 Johnston F D., and Overy D C Vibration ... frequency over the precordium, Circulation 3 ...
2 Gleichman U Both, A and Kreuzer H Qua... of force and rate of force development of pre... movement (apexcardiogram) Proceedings of th... European Congress of Cardiology Athens, 19...
3 Willems J L. Kesteloot H., and De Geest H. ... of acute hemodynamic changes on the apexcardi... dogs Am. J Cardiol. 29 ...04 197?
4 Denef B De Geest H., and Kesteloot H. ... change in myocardial contractility on the heig... slope of the calibrated apexcardiogram, Am. J C... 32 662 1973
5 Denef B Popeye R De Geest H and Kes... On the clinical value of calibrated displacement ... diography Circulation 51 541 19..
6 Duebel, H P., Guenther K. H and Witte J ... unf Differentiate Apexkardiographie ... bei Herz Kreislaufgesunden Dtsch. Gesundh... 30 582 197.
7 Reale A. Evaluation of the contractile state of ... human heart from the first derivative of the apexc... gram Circulation 36 933 1967
8 Vetter W R Sullivan R W and Hyatt, K ... Assessment of quantitative apexcardiography ... valive index of left ventricular function, Am. J Card... 29 667 1972
9 Manolas, J Wirz P., and Rutishauser W Relations... between duration of systolic upstroke time of apexcardio... gram and internal indexes of myocardial function ... man AM HEART J 91 7?6 19 6
10 Mason D T Sonnenblick, E H., Ross J Jr Co... J W., and Braunwald E Time to peak dp dt ... measurement for evaluating the contractile state of ... human heart (Abstr) Circulation 32(Suppl) II ... 1965
11 Fincker J L. Arnold P., Brandt C Vergnes, R. ... Meter P Effets compares de l isoproterenol, du ... gon de l angiotensin et du nitrate d amile sur la d... première du cardiogramme apexien, Arch. Mal Co... 66 8.. 1973

IMPORTANT
INFORMATION FOR AUTHORS

All manuscripts for the AMERICAN HEART JOURNAL should be sent to

Dean T Mason M D
Section of Cardiovascular Medicine
University of California
School of Medicine
Davis California 95616

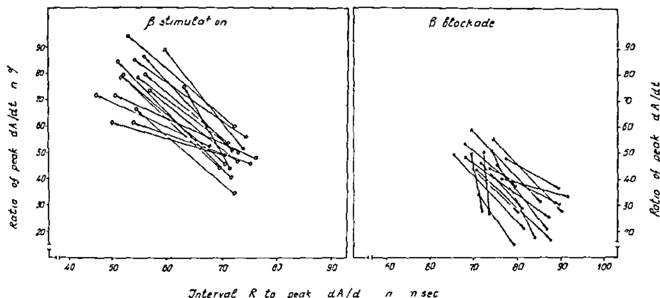


Fig 4 Variations of the ratio of the peak of the first derivative of the apexcardiogram to total derivative expressed as a percent and interval R to peak dA/dt expressed in msec during isoprenaline infusion and after propranolol *The arrows* point to values obtained after pharmacological intervention There is a strong reciprocal correlation between changes in the height of the peak dA/dt and the interval R to peak dA/dt The near parallelism of the curves indicates similar rates of change for both factors in all patients.

variation in the contractile state was confirmed with similar methods Mason and colleagues found that when the myocardial contractile state was enhanced by orciprenaline infusion there was an evaluation of peak dp/dt Conversely when contractility was depressed by beta adrenergic blockade most patients showed a lower peak dp/dt

The precise experiments in dogs by Willems and colleagues[3] during the effects of different interventions established the changes in amplitude of the calibrated dA/dt expressed as a percent of the controls They found a 60% elevation of the dA/dt provoked by isoprenaline and a decrease by 40% after propranolol Denef and associates[4] reported that in dogs positive inotropic interventions provoked a marked increase in peak dA/dt whereas negative inotropic agents had the opposite effect furthermore they found a fairly good correlation between these changes and changes of left ventricular dp/dt after the same pharmacological interventions Similar results were obtained clinically[5]

Mason and co workers measured the interval from electrical stimulation to peak dp/dt and assumed that it expressed the duration of the development of maximal tension in the ventricle They found that the same interval was inversely related to the contractile state in the isolated muscle strip and also that it was independent of preload and afterload Several authors[5, 7, 8] investigated the interval from the onset of ventricular depolarization to the peak of the first derivative of the apexcardiogram and found that the interval R to peak dA/dt has the same significance as the interval R to peak dp/dt It has been demonstrated that the interval R to peak dA/dt increased after beta adrenergic blockade[7] and shortened when the patient was given a beta adrenergic agonist[5, 7, 11] Other authors established an elongation of the same interval in patients with left ventricular failure due to atherosclerotic coronary heart disease and a close correlation between the interval R to peak dA/dt and the ejection fraction[8]

In conclusion our findings relative to changes of the interval R to peak dA/dt are in agreement with the investigations of several authors[5, 8] The proposed ratio of peak dA/dt to total amplitude of the derivative avoid the difficulties in calibrating the apexcardiogram and its first time derivative and simultaneously using the ratio of peak dA/dt and interval R to peak dA/dt permits a more complete noninvasive evaluation of the contractile state of the left ventricle from the peak dA/dt

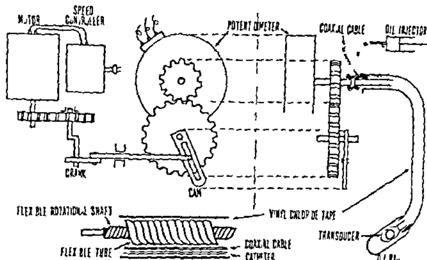


Fig 1 Diagrammatic illustration of the transesophageal sector scanner A small transducer in the esophagus is alternately rotated by a flexible rotational shaft and motor at 6 to 25 Hz (12 to 50 fields/sec) Although the small transducer is rotated alternately with great speed, there is little movement of the external flexible tube or oil bag, minimizing irritation or trauma to the esophagus

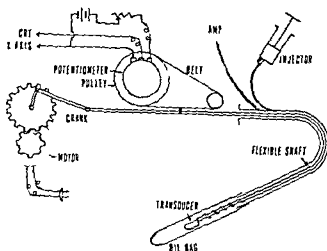


Fig 2 Diagrammatic illustration of the transesophageal linear scanner A small transducer in the esophagus is moved up and down by the flexible shaft and motor at 4 to 10 Hz (8 to 20 fields/sec)

continuously by phase control of alternating voltage using thyristors Maximum selective pulse repetition frequency is 6 0 KHz The field of view varies in depth from 10 cm to 17 cm according to the pulse repetition frequency The sector angle varies from 60 degrees to 180 degrees by changing a connecting point of a cam (Fig 1) Thus horizontal images of the entire adult heart can be obtained with this scanner Although the transducer is rotated at a high frequency the external flexible tube is stable within the esophagus Moreover the enveloping oil bag minimizes trauma to the esophagus (Fig 1) To identify the echo source of the cross sectional image a particular scan line is manually selected and B mode is switched to M mode to obtain M mode esophageal echograms

Linear scanner In order to obtain vertical images of the heart a transesophageal mechanical linear scanner was developed Fig 2 shows a diagram of the linear scanner A small transducer (transducer specifications as in the transesophageal sector scanner) is moved up and down in the esophagus by a flexible shaft and a motor at a rate of 4 to 10 Hz The plane of the scan is vertical through the center of the esophagus As shown in Fig 2 a potentiometer is rotated simultaneously with the transducer and monitors its position The signals detected by the transducer are amplified and displayed on a CRT as B-mode so that the position of an individual scan line corresponds exactly to the position of the transducer at the same instant Thus vertical cross sectional heart images are displayed in rectangular format on a CRT at a rate of 8 to 20 fields/sec The movement of the transducer can be varied from 2 5 cm to 8 cm by changing the crank Pulse repetition frequency and depth of field are as in the sector scanner

Recording methods A Polaroid camera, 35 mm still camera 8 mm movie camera and 16 mm movie camera can be utilized for the recording

Examination technique This system was est

Transesophageal cross-sectional echocardiography

Kohzoh Hisanaga M D
Asako Hisanaga B S
Kazuhiko Nagata M D
Yoshiyasu Ichie, M D
Nagoya Japan

Real time cross sectional echocardiography has proven useful for diagnosis of certain cardiac diseases and several imaging systems have been developed[1-7] However because the heart is observed through a small echo window on the chest wall the area which can be observed is considerably restricted In addition it is sometimes difficult to obtain heart images of diagnostic quality in patients with chronic obstructive pulmonary diseases barrel chest and obesity In order to minimize these limitations and to observe a wider area of the heart we developed a transesophageal high speed scanning system which can obtain cross sectional heart images without hindrance from ribs sternum and lung

Methods

The scanning system employs two kinds of hand held mechanical scanners each having a flexible tube and small ultrasonic transducer contained within a small oil bag which allows easy swallowing by adults One is a sector scanner which obtains horizontal images of the heart and the other is a linear scanner which obtains vertical images of the heart These scanners are used in conjunction with an improved Toshiba SSL 51H system which was originally developed as a transchest wall mechanical sector scanner

From the Department of Internal Medicine Mitsubishi Nagoya Hospital, and the First Department of Internal Medicine Nagoya University School of Medicine Nagoya, Japan

Received for publication Feb 28 1979
Accepted for publication Aug 16 1979

Reprint requests Dr Kohzoh Hisanaga Dept of Internal Medicine Mitsubishi Nagoya Hospital, 48 Sotodoi-cho Atsuta ku Nagoya 4 6 Japan.

Sector scanner The sector scanner consists of a motor (single phase commutator type) which can control the speed of rotation an iron flexible tube containing a flexible rotational shaft and a small transducer which is enclosed in an oil bag (15 mm diameter) (Fig 1) The specifications of the transducer are 2.25 MHz or 3 5 MHz 10 mm diameter and 7 5 cm focus The transducer is mounted in a 12 mm by 20 mm by 6 mm casing with rounded edges for easy esophageal passage, and is positioned at the tip of the flexible rotational shaft The flexible rotational shaft is enclosed in the iron flexible tube which has a diameter of approximately 8 mm and the latter is then wrapped with vinyl chloride tape The patients can easily swallow the flexible tube and shaft The oil bag which covers the transducer can be filled with oil by means of an injector The small transducer in the esophagus is rotated alternately by the flexible rotational shaft and the motor at a rate of 6 to 25 Hz The ultrasonic beam is alternately swept to the left and to the right so that the plane of the scan is perpendicular to the esophagus and the resultant images are displayed in a circular format The position of the transducer in the esophagus is continuously detected by a potentiometer which is connected directly to the flexible rotational shaft The signals of reflected echoes are displayed on a cathode ray tube (CRT) as B mode so that the angle of an individual scanning line is equal to the angle of the transducer at the same instant In this way horizontal cross sectional heart images are displayed on a CRT at a rate of 12 to 50 fields/sec Since a single phase commutator motor is employed the motor speed can be varied

0002-8703/80/110605 + 05$00 50/0 © 1980 The C V Mosby Co

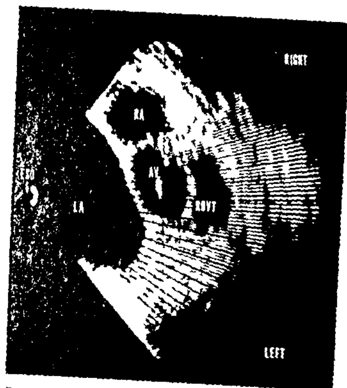


Fig 4 Horizontal scan at the level of the aortic valve as in Fig 3 The aortic cusps are closed in diastole Large left atrium is seen Right ventricular outflow tract is seen anterior to the aorta AV = aortic valve RVOT = right ventricular outflow tract



Fig 5 Transesophageal vertical linear scan through the pulmonary artery in another normal subject Bifurcation of pulmonary artery and part of ascending aorta are seen AO = aorta PA = pulmonary artery BI = bifurcation of pulmonary artery

utilize a transducer of higher frequency increasing resolution of heart images remarkably Unlike conventional external echocardiograms this system can continuously record heart images from the base to the apex as the transducer is being withdrawn or advanced in the esophagus Furthermore because of the wider sector angle entire horizontal heart images can be easily observed at the level of the atrioventricular valves The bifurcation of the pulmonary artery could be readily observed during vertical scanning However the area above the bifurcation of the pulmonary artery could not be seen because of interference from the trachea In addition it is easier to obtain M mode esophageal echograms while locating the various cardiac structures utilizing B mode echocardiography

We have found that the insertion of the transducer for recording heart images through the esophagus is no more difficult than inserting a commercially available gastrofiberscope The small flexible tube and transducer are easily swallowed and occasional gagging is usually so mild that the examination is hardly interrupted Although the transducer is moved rapidly there is no loss of esophageal wall contact nor is there esophageal trauma since the oil bag covers the transducer

Limitations of the described system include (1) fewer scanning planes (horizontal and vertical) available in comparison with conventional surface methods and (2) bubbles which may reduce image resolution occasionally form in the oil bag during linear scanning However current modifications and developments are devoted to overcoming these limitations[11]

In conclusion transesophageal cross sectional echocardiographic examination can be performed safely and the described system provides high resolution echoes of major cardiac structures in both horizontal and vertical scans There is little difference in the image quality among such scans Although this method is in an early stage of development we believe that in the future tran-

uated in 31 adult subjects (average age 36 4 years range 20 to 73 years average height 165 2 cm average body weight 58 7 kilograms) Prior to examination the patients usually received 0 5 mg of atropine sulfate and 10 mg diazepam intra muscularly and 3 g of lidocaine jelly orally The patients throats were sprayed with 4% lidocaine liquid Lidocaine jelly was applied to the oil bag and flexible tube in order to minimize discomfort and the loss of contact with the esophageal wall

Subjects usually swallowed the oil bag volun tarily and as easily as a commercially available esophageal fiberscope Oil was then injected into the bag through an external catheter in order to obtain good contact with the esophageal wall

Insertion of the transducer and transesopha geal ultrasound examinations were usually per formed with subjects in the left lateral or supine positions

Results

Following insertion to the 30 to 40 cm level good quality cross sectional heart images were observed in all 31 subjects All major cardiac structures were observed by withdrawing and advancing the transducer in the esophagus Com plete horizontal heart images were observed from the level of the atrioventricular valves (Fig 3) and the aortic valve (Fig 4) Vertical scanning demonstrated cardiac structures from the level of the aorta to the bifurcation of the pulmonary artery (Fig 5)

Discussion

Since B mode echocardiography has been applied to diagnosis of cardiac disease it has proven useful in anatomical and functional assessment of the heart and several real time imaging systems have been developed Bom and colleagues and King[3] have described multi trans ducer linear scanning systems which display heart images in a rectangular format whereas Griffith and Henry Eggleton and associates and Nishimura and co workers utilized mechan ical sector scanning of a single transducer to produce real time heart images On the other hand Somer and Von Ramm and Thurstone developed sector scanning systems to rely on phased array principles without the necessity of mechanical motion However thoracic configura tion excessive chest wall tissue or air containing

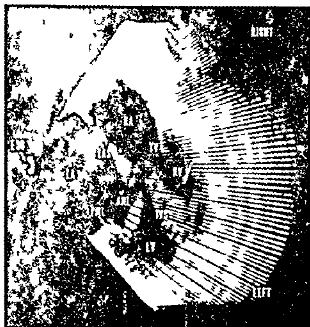


Fig 3 Transesopha eal horizontal sector scan during dias tole at the level of the mitral and tricuspid valves in a patient with severe mitral stenosis Tricuspid valve mitral valve ventricles and atria are seen Anterior and posterior mitral leaflets are thickened. *ESO* = esophagus *LA* = left atrium *RA* = right atrium *LV* = left ventricle *RV* = right ventri cle *IAS* = interatrial septum *IVS* = interventricular sep tum *AML* = anterior mitral leaflet *PML* = posterior mitral leaflet *TV* = tricuspid valve

lung may often limit the fields of view and resolution In order to minimize these limitations Frazin and colleagues have recorded M mode echocardiography through the esophagus using a small transducer which patients can swallow On the other hand Hisanaga and associates have developed a transesophageal pulsed Doppler echocardiographic system Although these meth ods are useful they do not provide two dimen sional cardiac images

We developed a transesophageal cardiac imag ing system which can obtain heart images with out hindrance from ribs sternum and lung Transesophageal echocardiography provides a wider area for study of the heart than that available using a conventional external system Heart images are observed through esophageal tissue in which ultrasound absorption is very low Therefore there is little difference in the image quality among various subjects In clinical exam inations one could obtain heart images with very low gain amplitude Thus one might potentially

Constituents of the human ventricular myocardium Connective tissue hyperplasia accompanying muscular hypertrophy

G William Moore MD PhD*
Grover M Hutchins MD
Bernadine H Bulkley MD
Jennifer S Tseng BA
Ping F Ki BS
Baltimore Md

The ease with which blood enters and distends the cardiac ventricles during diastole is related to the compliance or stiffness of the ventricular wall When the wall is stiff a greater energy must be present in the entering blood to produce the same degree of ventricular filling as is produced by blood under lower pressure when the wall has normal compliance It is the pressure energy of this blood entering the ventricles that when pathologically elevated may lead to the signs and symptoms of congestive heart failure Thus decreased compliance of the ventricular wall may be a cause of congestive heart failure

The compliance stiffness or tensile stress resisting capacity of the myocardium probably reflects the summation of the mechanical properties of its constituent muscle and interstitial connective tissue Muscle cells themselves will vary in the deformity or strain produced by an applied stress that is their elasticity depends on their state of contraction When muscle is relaxed its compliance is high—i.e it extends readily under an applied tension[2] T

pliance of the interstitial connective
largely a function of the collagen fib
they contain Collagen appears to exis
tissues in an irregularly coiled or tang
which resists tension only moderately
the fibers are extended whereupon its
changes markedly and it becomes highly
to further elongation[3]

The present study was undertaken t
gate the impression that when hypertro
cardiac muscle cells develops in respons
pathological process there is concomitan
disproportionate increase in the interst
nective tissues Composition of the m
wall was quantitated histologically in
group of hearts with normal coronary ar
the values were compared by correlati
cients with other features of the cases.
studied included normal hearts and th
abnormalities that could be expected to
increased heart wall thickness both
without chamber dilatation The result
that cardiac muscle cell hypertrophy i
accompanied by increase in connective
that the proportion of myocardium con
connective tissue remains unchanged.

Materials and methods

Patients listed in the autopsy files of T
Hopkins Hospital whose hearts had bee
following postmortem arteriography an
in distention[4] were reviewed A case was
in this study if a technically satisfactor

From the Department of Pathology and the Cardiovascular Division of the Department of Medicine The Johns Hopkins Medical Institutions, Baltimore Md

Supported by Grants 5 P50-HL 1 [illegible] and HL-22963 from The National Institutes of Health Public Health Service Department of Health, and Human Services

Received for publication June 29 1979

Accepted for publication Nov 4 1979

Reprint requests Dr G William Moore Dept of Pathology The Johns Hopkins Hospital Baltimore Md 1205

Dr Moore is a Research Fellow of the American Heart Association Maryland Affiliate In

0002-8 03/80/110610 + 0 $00.0/0 © 1980 The C V

esophageal cross sectional echocardiography will be useful for cardiac diagnosis in the patient with nondiagnostic transthoracic echoes

Summary

A transesophageal cardiac imaging system is described This system employs hand held mechanical sector and linear scanners each having a flexible tube and a small ultrasonic transducer contained within a small oil bag easily swallowed by adults In the sector scanner a small transducer in the esophagus rotates alternately and horizontal heart images are displayed In the linear scanner a small transducer in the esophagus moves up and down and vertical heart images are displayed The system was evaluated in 31 adult subjects In all subjects stable high quality heart images were observed continuously from base to apex as the transducer was being withdrawn or advanced in the esophagus In horizontal scans entire heart images were observed at the level of the atrioventricular valves In vertical scans the bifurcation of the pulmonary artery could be observed clearly There was little difference in the image quality among subjects

REFERENCES

1 Somer J C Electronic sector scanning with ultrasonic beams Proceedings of the First World Congress on Ultrasound Diagnostic in Medicine June 2 7 1969 Vienna Austria

2 Bom N Lancee C T Van Zwieten B Kloster F E and Roelandt J Multiscan echocardiography I Technical description Circulation 48 1066 1973

3 King D L Real time cross sectional ultrasonic imaging of the heart using a linear array multi-element transducer J Clin Ultrasound 1 196 1973

4 Griffith J M and Henry W L A sector scanner for real time two-dimensional echocardiography Circulation 49 1147 1974

5 Eggleton R C Dillon J C Feigenbaum H D Johnston K W, and Chang S Visualization of cardiac dynamics with real time B mode ultrasonic scanner (Abstr) J Clin Ultrasound 2 222 1974

6 Von Ramm O T and Thurstone F L Cardiac imaging using a phased array ultrasound system I System design Circulation 53 258 1976

7 Nishimura K, Hibi N Kato T, Fukui Y Arakawa T Tatematsu H Miwa A Tada H Kambe T Nakagawa K and Takemura Y Real time observation of cardiac movement and structures in congenital and acquired heart diseases employing high speed ultrasonocardiotomography AM HEART J 92 340 19 6

8 Frazin L Talano J V Stephanides L Loeb H S, Kopel L and Gunnar R M Esophageal echocardiography Circulation 54 102 1976

9 Hisanaga K Hisanaga A Ichie Y Nishimura K Hibi N Fukui Y, and Kambe T Transesophageal pulsed Doppler echocardiography Lancet 1 53 1979

10 Hisanaga K and Hisanaga A A new real time sector scanning system of ultra wide angle and real time recording of entire adult cardiac images—Transesophagus and trans chest wall methods *in* White D and Lyons E A eds Ultrasound in medicine Vol 4 New York 1978 Plenum Press, pp 391-402

11 Hisanaga K Hisanaga A and Ichie Y A transesophageal ultrasound sector scanner for oblique scans (Abstr) Circulation 60 (Suppl II) II 245 1979

Table I Muscle cell percentage and nuclear density of the ventricular myocardium*

Group	Number	Age (years)	Heart weight (grams)	Diagnosis of congestive heart failure	Right ventricle		Interventricular septum		Lef
					Muscle cell nuclei per grid area	Muscle cell percent of myocardium	Muscle cell nuclei per grid area	Muscle cell percent of myocardium	Muscle cell nuclei per grid are
Normal	33	52 ± 18 (17 87)	332 ± 57 (220-430)	0	19 ± 8 (8 38)	76 ± 8 (57 92)	19 ± 7 (6 35)	76 ± 8 (46-90)	18 ± 8 (9 30)
LVH	28	52 ± 18 (17 77)	636 ± 176 (405 1 230)	12	17 ± 4 (10 26)	75 ± 4 (63 88)	15 ± 6 (4 26)	77 ± 7 (62 90)	13 ± 5 (7 ?4)
RVH	25	52 ± 15 (17 83)	440 ± 108 (200 700)	12	17 ± 6 (7 28)	73 ± 7 (58 84)	19 ± 8 (8-37)	6 ± 11 (58 94)	17 ± 6 (10-?8)
Chronic dilatation	41	50 ± 17 (18 88)	730 ± 200 (380 1 200)	37	15 ± 5 (6 26)	74 ± 9 (51 90)	15 ± 6 (8 30)	73 ± 10 (55-93)	14 ± 6 (6-37)
Total	127	51 ± 17 (17 8?)	552 ± 224 (200 1 230)	61	17 ± 6 (6 38)	74 ± 8 (51 9?)	17 ± 7 (4 37)	75 ± 9 (46 94)	16 ± 7 (6-37)

Mean ± standard deviation (range)
$p < 0\ 01$ $p < 0\ 05$ (Student s t test) compared to normal

method A grid with 36 intersection points in one 10 power ocular of a binocular microscope was positioned randomly over areas of the myocardial region being studied histologically and the type of tissue each point lay on was determined (Fig 1) Points which fell on empty spaces in the section created as artifacts of preparation were excluded Such points usually amounted to about 15% of the total Intersections falling on cardiac muscle cell sarcoplasm or nucleus were called muscle and all other points not on artifactual empty space were considered connective tissue Between three and six grid settings were evaluated for each area of myocardium using the 25 power objective lens The grid covered an area of 0 016 mm Areas to be counted were chosen by scanning the slide under low magnification within this area fields to be counted were randomly selected The reproducibility of the determinations in serial counts and in blind recounting of slides was excellent rarely greater than 10% difference between counts

The density of cardiac muscle cell nuclei was determined for each of the three areas of myocardium for which the percent of constituents had been determined Using the same ocular grid as above the number of cardiac muscle cell nuclei falling within the square were counted for a minimum of five randomly selected fields from right to left ventricular free wall and interventric ular septum Nuclei touching the upp margins of the grid were included tho the lower and right margins were exc reproducibility of counts on separate tions and the similarity of values o counts was excellent The counts expressed as nuclei per grid area (0 016 used for comparison only

In an effort to study the possib ischemia as the basis for alterations n nective tissue content of the ventricula dium diameter measurements were ma major epicardial coronary arteries In studies of these vessels it has been show cube of a parent vessel diameter appr equals the sum of cubes of the branc Thus in coronary arteries unaffected b sclerotic disease we can construct a theoretical single coronary artery wh eter cubed equals the sum of diameters the right and left coronary arteries In so the angiographic injection of the left m nary was unsatisfactory so this theoreti coronary artery was obtained from the diameters cubed of the right left ant scending and left circumflex coronaries.

Finally pairwise correlation coefficien son s r) were computed for all possible pa following 12 variables (1) age in years (weight in grams (3) body surface area in

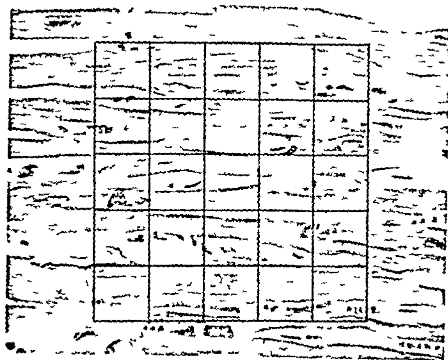


Fig 1 Left ventricular myocardium with superimposed ocular grid used for counting cardiac muscle cell nuclei and determining the myocardial constituents by point counting (Hematoxylin and eosin original magnification ×400)

gram revealed no vascular abnormality and gross examination of multiple transections of the epicardial coronary arteries showed at most only trivial atherosclerosis Cases with replacement fibrosis or amyloid infiltration that could interfere with the determinations were excluded

The coronary arteries were injected with a barium gelatin pigment mass at 100 to 150 mm Hg pressure The heart was then immersed in formalin and fixed in distention at 30 to 40 cm H_2O pressure by intracavitary formalin introduced through cannulae in the atria and great vessels After fixation stereoscopic radiographs were prepared of the intact heart and the transverse slices into which it was cut Multiple histological sections of the ventricular myocardium were prepared by routine processing sectioning and staining which at a minimum included left and right ventricular free wall and interventricular septum taken from transverse sections at the approximate level of the widest diameter of the left ventricle

Each case was assigned to a disease group based on the results of a previous analysis of the clinical and pathological features Normal applied to those cases with neither clinical nor pathological evidence of heart disease Cases designated LVH were those with left ventricular hypertrophy as the major finding usually secondary to aortic valve stenosis or systemic hypertension RVH categorized those cases with predominant right ventricular hypertrophy secondary to pulmonary hypertension as caused by mitral stenosis or pulmonary parenchymal disease Cases in the Chronic Dilatation group had left ventricular hypertrophy secondary to dilatation as for example with aortic or mitral regurgitation or idiopathic myocardiopathy Cases with features of more than one process were assigned to a group according to the predominant or primary abnormality The determination of the presence of congestive heart failure was made from the available clinical records of diagnoses of the clinicians caring for the patient during life

The gross and histological features of the ventricular walls were studied for each case The amount and distribution of interstitial connective tissue was noted for the free wall of right and left ventricle and septum for each heart The percent of myocardium in each of the three areas which consisted of muscle cell and of interstitial connective tissue was determined by a point count

Table II Correlations (Pearson's r) of significant paired variables ($p < 0.01$)*

	RV muscle cell nuclei per grid area	RV muscle cell percent of myocardium	IVS muscle cell nuclei per grid area	IVS muscle cell percent of myocardium	LV muscle cell nuclei per grid area	LV muscle [illegible] percent of myocardium
Heart weight	−0.38		−0.41		−0.43	
RV muscle cell nuclei per grid area			0.46		0.44	
RV muscle cell percent of myocardium						0.4[illegible]
IVS muscle cell nuclei per grid area					0.[illegible]6	
IVS muscle cell percent of myocardium						0.41
LV muscle cell nuclei per grid area						0.31

IVS = interventricular septum LV = left ventricle RV = right ventricle
*Nonsignificant correlations at the 0.01 level are not displayed. Results show that nuclear density and heart weight are negatively related.

is designed for individual correlations may overestimate the statistical significance of the correlations taken as a whole It was our intent not to neglect potentially significant linear relationships

Results

The major characteristics of the 127 patients with normal coronary arteries included in this study are shown by disease groups in Table I There were 33 normal hearts 28 hearts with left ventricular hypertrophy 25 hearts with right ventricular hypertrophy and 41 hearts with chronic dilatation The patients were all adults with comparable ages at death The normal hearts averaged 332 grams while the hearts with right ventricular hypertrophy left ventricular hypertrophy and chronic dilatation showed progressively larger abnormal weights None of the patients with normal hearts less than half with left and right ventricular hypertrophy and 90% of cases with chronic dilatation had a clinical history of congestive heart failure

The normal heart has a nuclear density (Table I) of about 1[illegible] per grid area in the interventricular septum and in both ventricular free walls but the larger diseased hearts namely those with left ventricular hypertrophy and chronic dilatation showed significantly decreased density of cardiac muscle nuclei (Student [illegible] t test) indicating that the cardiac mu[illegible] [illegible] increase in size rather than in number [illegible] contrast determinations of the percentage of [illegible] cell mass in relation to connective tissue [illegible] it remains relatively constant at 7[illegible]% of the myocardium in the thr[illegible] segments of the normal human ventricle and [illegible] not significantly altered in disease states wh[illegible] enlarge the heart

Pearson's r coefficient was calculated for [illegible] pairs of 12 measurements taken on each he[illegible] and is summarized in Table II Only r val[illegible] which were significant at the 0.01 level (Stud[illegible] t test) are displayed Wall thickness mea[illegible] ments correlated in parallel with heart wei[illegible] measurements and are not shown here We fo[illegible] that nuclear density in the three ver[illegible] segments is negatively related to heart wei[illegible] Other correlations in this table represent predi[illegible] able interrelationships of nuclear density or p[illegible] cent muscle to one another between the thr[illegible] different segments of the heart wall We have [illegible] explanation for the positive correlation betw[illegible] LV nuclear density and LV percent muscle [illegible] contrast heart weight is *not* correlated to perc[illegible] muscle in all three segments that is, $p > 0.0$[illegible] all three correlations We can summarize the[illegible] correlations by observing that as heart wei[illegible] increases myocardial muscle cell nuclear den[illegible] decreases showing that muscle hypertrophy occurs with cardiac enlargement By contrast the percentage of myocardium consisting of musc[illegible] does *not* change showing that commensura[illegible] connective tissue increase is a component of cardiac enlargement

In some hearts with dilatation and hyper[illegible] phy we observed a characteristic increase of connective tissue in the perivascular area [illegible] in Fig 2. This localized accentuation of co[illegible]

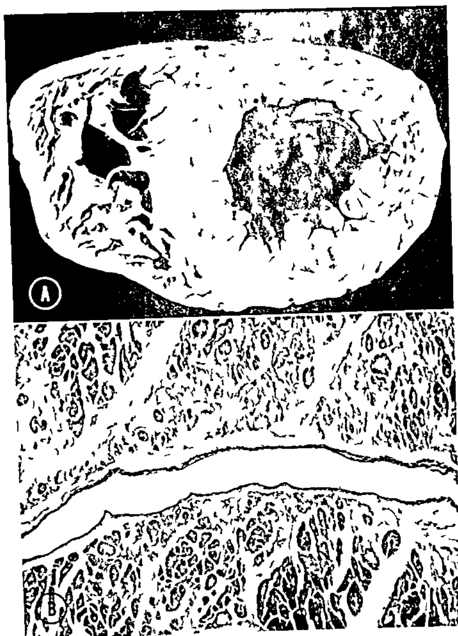


Fig 2 *A* Transverse section of the ventricles of a markedly enlarged heart with chronic dilatation. The left ventricular free wall myocardium on the right shows numerous striae of connective tissue running between the epicardium and endocardium. The striae are especially prominent in the mid part of the wall. *B* The striae are found to be an accumulation of interstitial connective tissue around blood vessels on histological examination. (Hematoxylin and eosin, original magnification ×75)

right ventricular free wall thickness in cm, (5) right ventricular free wall nuclear density per grid area, (6) right ventricular free wall percent muscle of myocardium, (7) interventricular septum thickness in cm, (8) interventricular septum nuclear density per grid area, (9) interventricular septum percent muscle of myocardium, (10) left ventricular free wall thickness in cm, (11) left ventricular free wall nuclear density per grid area, (12) left ventricular free wall percent muscle of myocardium. These correlation coefficients were used to identify the existence and direction (positive or negative correlation) of linear trends in the data. It is recognized that this calculation, which

shown by the distribution of the fibrosis *around* the larger intramyocardial arteries (expansive striae) and by correlations which suggest that the large epicardial coronary arteries increase in parallel with cardiac enlargement. Other workers have independently observed an increase in large coronary size with cardiac hypertrophy.

The evidence suggests that cardiac enlargement occurs by muscle cell hypertrophy and by maintenance of a uniform proportion of interstitial connective tissue. The decrease in compliance or increased stiffness associated with congestive heart failure may in some cases result from a simple increase in wall thickness of the myocardium.

Summary

Left sided congestive heart failure may be secondary to decreased left ventricular myocardial compliance in some patients. To investigate the anatomic basis for altered wall stiffness, morphometric determinations of muscle cell nuclear density and percent of myocardium consisting of muscle cells were made for right and left ventricular free wall and septum in 127 hearts with normal coronary arteries. The hearts were normal (33 patients), had left ventricular hypertrophy (28 patients), right ventricular hypertrophy (25 patients), or chronic dilatation (41 patients). With cardiac enlargement the average percent of myocardium consisting of muscle did not change from the approximately 75% value characteristic of normal hearts. In contrast, muscle cell nuclear density decreased proportionate to cardiac enlargement, demonstrating that muscle cell hypertrophy, not hyperplasia, is the basis for weight increase. Some hearts with marked long standing dilatation also had perivascular and interstitial striae of connective tissue differing from replacement fibrosis. An increase in epicardial coronary artery caliber commensurate with increased heart weight suggests that ischemia is not the basis of connective tissue increase. The results show that cardiac muscle cell hypertrophy is accompanied by commensurate increase in interstitial connective tissues. This pattern of myocardial growth with cardiac enlargement may produce increased myocardial stiffness simply as a result of increased wall thickness and may lead to left sided congestive heart failure.

REFERENCES

1. Levine H J. Compliance of the left ventricle, (Editorial) Circulation 46 423 1972.
2. Laird J D. Asymptotic slope of log pressure vs log volume as an approximate index of the diastolic elastic properties of the myocardium in man, Circulation 53 443 1976
3. Burton A. C. Walls of the blood vessels and their function in Physiology and Biophysics of the Circulation. An Introductory Text, Chicago 1969 Year Book Medical Publishers Chapter 7 pp 77-83.
4. Hutchins G M and Anaya O A. Measurements of cardiac size, chamber volumes and valve orifices at autopsy. Johns Hopkins Med. J. 133 96, 1973.
5. Dunnill, M S. Quantitative methods in the study of pulmonary pathology. Thorax 17 320 1962.
6. Hutchins G M and Vie S A. The progression of interstitial myocarditis to idiopathic endocardial fibroelastosis, Am. J Pathol. 66 483 1972.
7. Hutchins, G M, Miner M. M and Boitnott, J K. Vessel caliber and branch angle of human coronary artery branch points. Circ. Res. 38 572, 1976.
8. Bishop S P and Cole C R. Ultrastructural changes in the canine myocardium with right ventricular hypertrophy and congestive heart failure. Lab Invest 20 1969
9. Linzbach A J. Heart failure from the point of view of quantitative anatomy. Am J Cardiol. 5 370 1960
10. Adler C P and Sandritter W. Numerische Hyperplasie der Herzmuskelzellen bei Herzhypertrophie. Dtsch Med Wochenschr 96 1895 1971
11. Bishop S P. Effect of aortic stenosis on myocardial cell growth, hyperplasia and ultrastructure in neonatal dogs, in N S Dhalla ed., Recent Advances in Studies on Cardiac Structure and Metabolism vol. 3, Myocardial Metabolism, Baltimore 1973 University Park Press, pp 637-656
12. Bishop S P and Hine P. Cardiac muscle cytoplasmic and nuclear development during canine neonatal growth, in Recent Advances in Studies on Cardiac Structure and Metabolism vol 8, The Cardiac Sarcoplasm, P E Roy and P Harris, eds. Baltimore 1975 University Park Press pp 77 98
13. Bartošova D., Chvapil M., Korecky B, Poupa, O., Rakusan K, Turek, Z. and Vizek, M. The growth of the muscular and collagenous parts of the rat heart in various forms of cardiomegaly. J Physiol. 200 1969
14. Lindy S., Turto H and Uitto J. Protocollagen proline hydroxylase activity in rat heart during experimental cardiac hypertrophy. Circ Res. 30 205 1972
15. Edgren J, von Knorring J., Lindy S and Turto, H. Heart volume and myocardial connective tissue during development and regression of thyroxine induced cardiac hypertrophy in rats. Acta Physiol Scand 97 514 1976
16. Fuster V, Danielson M A., Robb R. A, Broadbent J C, Brown A L Jr and Elveback L R. Quantitation of left ventricular myocardial fiber hypertrophy and interstitial tissue in human hearts with chronically increased volume and pressure overload. Circulation 55 504 1977
17. Harrison C V and Wood P. Hypertensive and ischaemic heart disease. A comparative clinical and pathological study. Br Heart J 11 205, 1949

tive tissue may contribute to increased stiffness of the myocardium in some hearts That these so called expansive striae are indeed part of the growth process in cardiac enlargement rather than fibrosis secondary to chronic ischemia is suggested first by their location namely in the distribution of nonatherosclerotic blood vessels which would least likely be ischemic The lack of an ischemic basis is further supported by correlations of coronary diameter and other variables measured in this study The diameter of the theoretical coronary is shown in Table III correlated to heart weight and wall thickness and nuclear density of the interventricular septum and left ventricular free wall These correlation values are all significant at the 0 01 level The most striking finding is the positive correlation between diameter of the theoretical coronary with heart weight This suggests that as the heart enlarges total coronary blood flow in these patients grows concurrently to accommodate the needs of the myocardium The increase of coronary flow with increased interventricular septum and left ventricular free wall thickness likewise suggests that the enlarged hearts in our series developed compensatory blood flow As previously demonstrated a decrease in the nuclear density parallels cardiac hypertrophy and likewise correlates with increased coronary flow All these correlations support the concept that the enlarged hearts in this series stimulate the necessary blood flow and do not develop increased connective tissue on the basis of ischemia

Table III Variables significantly correlated (Pearson s r) to the diameter of the theoretical coronary artery ($p < 0\ 01$)*

Variable	r
Heart wei ht (grams)	0 57
IVS wall thickness (cm)	0.33
IVS muscle cell nuclei per grid area	–0.31
LV wall thickness (cm)	0.29
LV muscle cell nuclei per grid area	–0 30

IVS = interventricular septum LV = left ventricle
*Nonsign ficant correlations at the 0 01 level are not displayed Results show that coron ry lum n size increases with increasin heart weight.

Discussion

Many patients with enlarged ventricles develop congestive heart failure One explanation for this congestive failure may be a decreased compliance of the ventricular myocardium In this study we examined 127 hearts from autopsied patients with normal coronary arteries and no destructive or infiltrative myocardial lesions About half the patients in the study carried a clinical diagnosis of congestive heart failure and had enlarged hearts at autopsy With cardiac enlargement cardiac muscle cells were found to increase in size while the proportion of connective tissue remained unchanged The increase in weight of the adult heart predominantly by hypertrophy has been observed by other workers both experimentally in dogs and in autopsy studies of humans In infants and in neonatal dogs by contrast increase in heart weight occurs by hyperplasia Experimental evidence relating the amount of myocardial collagen to the degree of ventricular enlargement has been equivocal In hypertrophy caused by valvular disease the content of myocardial collagen increases[3] whereas in thyroxine induced hypertrophy the total collagen decreases[3] Thus a mechanically induced ventricular hypertrophy may decrease ventricular wall hypertrophy by increasing total collagen while a metabolically mediated collagen loss may allow the ventricles to dilate because of increased compliance The human hearts in the present series appear to be more closely akin to the mechanical interpretation

Similar quantitative studies of the myocardial constituents were performed on autopsied patients with chronic mitral incompetence and hypertensive heart disease[6] Myocardial fiber diameter and proportion of interstitial tissue were obtained from computer analysis of enhanced photographs These workers noted a somewhat higher proportion of interstitial tissue than we did (32% against our 25%) but this may be due to the avoidance in our method of large vascular spaces and artifactual tissue spaces They also found a more than proportionate increase in patients with severe mitral incompetence which may correspond to our qualitative observations of expansive striae in chronically dilated hearts These workers found a diffuse hypertrophy in both groups of diseased hearts similar to our observations

It could be argued that the increase in perivascular connective tissue seen in some enlarged hearts in this study is mostly ischemic in nature with the hypertrophied myocardium outrunning its blood supply That this is not the case is

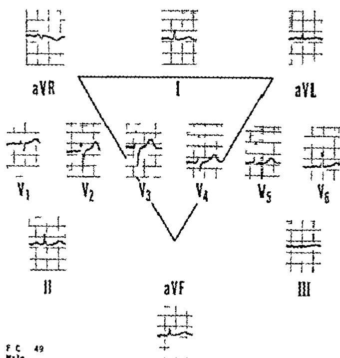


Fig 1 The ECG of a 49 year old male patient with a six month history of angina pectoris The treadmill test was positive the myocardial scan showed absent septum perfusion and coronary angiography revealed occlusion (100%) of the LAD at its origin and 95% narrowing of the principal diagonal at its origin

grams electrocardiograms and clinical records of 274 patients studied at Loma Linda University Medical Center Loma Linda California over a four year interval were analyzed The series with obstructive coronary artery disease consisted of 178 patients with chest pain most of whom had greater than 70% estimated cross sectional obstruction in one or more coronary arteries The ECGs of 96 patients without angiographic evidence of obstructive coronary artery disease were reviewed for ECG changes of the syndrome

A 12 lead electrocardiogram recorded on a high sensitivity paper was examined by two observers for absence of Q waves in Leads 1 aV_L V_5 and V and evidence of myocardial ischemia and/or infarction Records showing absence of Q waves with clockwise rotation on the long axis right or left bundle branch block and bilateral bundle branch block were excluded Some patients were exercise stressed on a computer controlled treadmill with three minute work loads beginning with 1 7 MPH at a 5% grade increasing to 1 7 MPH at a 10% grade 2.5 MPH a 12% grade 3 4 MPH at a 14% grade and MPH at a 16% grade The exercise was contin up to the point of fatigue chest pain or dysp Heart rate arterial pressure ECG morphol and symptoms were continuously monito throughout Exercise stress testing was not d on patients with recent acute myocardial pa

Selective coronary arteriography was car out by the Judkins technique[3] Ventriculogra was performed and recorded in the RAO degree and LAO 20 degree projections u biplane cineradiography The coronary arte were imaged in the AP RAO 20 degree LAO degree lateral and LAO craniocaudad pro tions using 35 mm cineradiography and 100 m photofluorography

The extent of artery narrowing was estima from the multiprojection views of the coron arteries The narrowing was expressed as a p cent cross sectional obstruction and the agr ment among different arteriographers of t extent of narrowing was remarkably close.

In analyzing the topography of obstruct coronary artery disease the major coron arteries were divided into proximal mid a distal regions For the left anterior desce d the region from the origin to the take-off of t first septal perforator was designated proxim the region extending from the first septal perf tor to the take off of the second anterior l ventricular branch (second diagonal) was cal the mid and the remaining artery was called t distal region The proximal region of the circu flex artery extended from its origin to the take of the obtuse marginal artery the mid reg extended from the obtuse marginal to the pos olateral left ventricular artery or posterior d scending artery and the distal segment extend to the remaining posterior continuation(s) of t circumflex The proximal region of the ri coronary extends from the take off to the ac marginal artery the mid region extends from t acute margin to the posterior descending and t posterior descending extends as the distal co uation of the artery

In some patients following coronary arter raphy 99m technetium microspheres 2.6 to 3 µCi were injected into the left coronary arte and 131 1 macroaggregated albumin 131 to 1 µCi were injected into the right coronary arter Other patients received differing amounts of 99

Coronary arteriograms and myocardial scintigrams in the electrocardiographic syndrome of septal fibrosis†

Renzo Romanelli M D *
William H Willis Jr M D **
Winston A Mitchell M D ***
Robert J Boucek M D ****
Miami Fla and Loma Linda Calif

In 1956 Burch[1] described the absence of Q waves in Leads 1 V_5 and V_6 in electrocardiograms (ECG) without left bundle branch block or clockwise rotation of the heart and introduced the ECG syndrome of septal fibrosis This description was followed by a necropsy study of 1 184 hearts 127 of which had histologic evidence of septal fibrosis[2] One hundred and one of the 127 hearts had the ECG syndrome of septal fibrosis only 2% had the ECG syndrome without morphologic evidence of septal fibrosis Subsequently other authors substituted the term left septal block for the ECG syndrome of septal fibrosis

Witham surveyed 200 patients with classical angina pectoris and identified 40 patients with nondiagnostic ECGs The vectorcardiograms (VCGs) of these 40 patients could be divided into seven patterns each of which identified myocardial infarction One of these patterns was the equivalent of Burch s ECG syndrome of septal fibrosis the Q loop of initial septal depolarization was absent and the abnormal initial vector in the horizontal and saggital planes extended beyond the expected time for completion of trans septal depolarization Witham considered this VCG abnormality as indicating septal infarction

As part of a continuing effort to refine the clinical assessment of coronary pathology we examined for relationships between obstructive coronary artery disease myocardial perfusion and the ECG syndrome of septal fibrosis in a series of patients studied with coronary arteriography and myocardial scintigraphy It was learned that patients with angina pectoris and the ECG syndrome of septal fibrosis have a higher incidence and a more extensive narrowing of the proximal LAD by obstructive coronary artery disease and a greater ventricular septal hypoperfusion than patients without the syndrome The fact that the ECG syndrome of septal fibrosis occurs in only 4% of age matched patients with angiographically determined coronary arteries free of obstructive disease strongly supports the usefulness of this ECG finding in identifying a subset of angina pectoris patients with a high probability of proximal LAD disease and left ventricular hypoperfusion

Materials and methods

The coronary arteriograms left ventricular cineangiograms myocardial perfusion scinti

From the Divisi n of Gerontology Departm nt of Med cine Uni ersity of Miami School of Med in Miami, Fla and th Card o ascular Laboratories D partments of Med c ne and Rad ology Loma Lind U i ers ty Scho l of M d cine Loma Lind Cal f

This in estig tion was supported in part by United States Publ Health Servic Research Grants HL-1 909 and HL 17865 f om th Natio al Heart a d Lung I titute

Recei ed for publ cati n July 30 1979

Accepted fo public t on O t 19 19 9

Reprint req ests R bert J B ucek M D (R1 7) Di is n of Gerontol gy Un ers ty of Miam School f Medici P O Box 016960 Miami, Fla 33101

*Visiting Professor Dept of Medicin Un rsity of M am School of Medicine Miami, Fla a d Professor f G ront l gy Un ers ty of Pisa, Pisa Italy

**Co-directo Card ovascula L borat ries Dept f Med cin Loma Lind Un vers ty School of Med cin Loma Lind Cal f

***Co-directo Card o ascular Lab rat ri D pt of Rad l gy Loma Lind Uni rsity School of Medi in

****Professor of Med ine a d Ch ef Divis n of Ge ntology D pt f Medicine U n rsity of Miami Sch l f Med cin Miam Fla

†This in estigation is dedi ated to D M l n P J dkins pionee n qu lity cor n ry rteriography

0002-8 03/80/110617 + 05$00 50/0 © 1980 The C V Mosby Co

Table III Atheromatous disease of the proximal left anterior descending artery and the ECG syndrome of septal fibrosis

Groups	Number	Frequency of ≥ 70% narrowing (%)	% narrowing
A + B	44	68	74 ± 6
C	48	45	54 ± 4
p		< 0 001†	A + B vs C – < 0 01‡

Mean ± standard error
Statistical probability † Student's t test ‡ Chi square test

patients in the three groups patients with the ECG syndrome of septal fibrosis (Groups A and B) had a mean narrowing of 74% in contrast to 54% for patients without the syndrome (Group C)

One hundred and forty six patients had myocardial scintigraphy 62 with and 84 without the ECG syndrome of septal fibrosis (Table IV) Nearly 60% of the patients with the ECG syndrome of septal fibrosis (Groups A and B) have abnormal perfusion of the ventricular septum as opposed to 23% of the patients without septal fibrosis (Group C) a highly significant difference ($p < 0\ 001$) The percentage of patients with abnormal perfusion of the remaining left ventricle may also be greater in patients with (Groups A and B) than in patients without the ECG syndrome of septal fibrosis (Group C) ($p < 0\ 05$)

As judged from the findings presented in Tables III and IV no differences in the proximal LAD pathology or in the extent of left ventricular hypoperfusion are seen in comparisons of Groups A and B patients

To determine the incidence of the ECG syndrome of septal fibrosis in individuals without angiographic evidence of obstructive coronary artery disease the ECGs of 96 randomly selected records from the Radiology Museum at Loma Linda were reviewed The patients presented with atypical angina like chest pain Out of these 96 patients only four had the ECG changes of septal fibrosis

Discussion

Sodi Pallares and colleagues in a definitive study on the depolarization activation of the ventricular septum in dogs reported the orientation of the initial QRS vector as proceeding from the left side (midway between the anterior and posterior edges of the septum at the juncture of the lower two thirds with the upper one third of the septal surface) towards the trabecular [illegible] and the apex of the right ventricle The L[illegible] muscle mass activated on the left side of [illegible] septum generates a voltage field that inscribe[illegible] Q wave in leads I aVL V4 V5 and V6 A [illegible] initial septal depolarization from left to r[illegible] occurs for the human heart and an absence [illegible] Q wave in Leads I aVL V4 V5 and V6 reflec[illegible] according to Goldman[3] a parallel orientation [illegible] the ventricular septum with respect to the ex[illegible] ing electrodes scarring of the middle third of [illegible] ventricular septum left bundle branch block [illegible] preexcitation syndromes where the initial f[illegible] proceed anteriorly from right to left

A positive correlation between the severity [illegible] obstructive lesions in the proximal LAD and [illegible] ECG syndrome of septal fibrosis (Table I[illegible] reflects the key role of the LAD in transpor[illegible] blood to the ventricular septum The reg[illegible] where the left bundle branch ramifies and [illegible] initial ventricular septal depolarization vec[illegible] commences is supplied by proximally loca[illegible] septal penetrating branches from the LA[illegible] Atheromatous lesions proximal to the first se[illegible] perforating branch causing a significant (< [illegible] luminal narrowing would therefore reduce [illegible] blood flow to the ventricular septum and ca[illegible] ischemic injury loss of myocardium and ul[illegible] mately fibrosis in the region of the penetrati[illegible] His Purkinje bundle responsible for the in[illegible] septal depolarization Group C patients on [illegible] other hand with a lower incidence and extent [illegible] critical proximal LAD narrowing would hav[illegible] reduced incidence of septal fibrosis

Finding approximately 60% of patients with [illegible] ECG syndrome of septal fibrosis having abnorm[illegible] ventricular septal myocardial scintigrams (Ta[illegible] IV) represents a positive correlation between [illegible] near 75% narrowing of proximally loca[illegible] obstructive LAD lesion (Table III) and reduc[illegible] blood flow to the ventricular septum This 6[illegible] value contrasts sharply with the 23% value f[illegible] Group C patients without the ECG syndrome [illegible] septal fibrosis and where the extent of atheroma[illegible] tous narrowing of the proximal LAD is only [illegible] (Table III)

A more extensive coronary pathology and [illegible] ventricular hypoperfusion might have been pr[illegible] dicted for Group B as compared to Group [illegible] patients with the ECG syndrome of septal fibro[illegible] sis The fact that the two groups are ind[illegible] guishable by the various examinations includ[illegible] this study points up the serious implicatio[illegible]

Table I Patients with and without the ECG syndrome of septal fibrosis

Groups	Number	Age	Sex		Duration of angina (months)	Stress testing		
			M	F		Negative	Positive	%
A	30	56.5 ± 1.45	26	4	28.83 ± 7.52	2	22	91
B	35	59.5 ± 1.5[illegible]	29	6	23.14 ± 6.[illegible]4	0	14	100
C	113	57.0 ± 0.77	95	18	36.52 ± 4.50	25	43	63
D	96	49.5 ± 1.62	52	44	—	—	—	—

Mean and ± standard error

technetium microspheres injected down the two coronary arteries At the end of the injections the patient was taken to the Nuclear Medicine Section and multiple views with an Anger camera were integrated in a data acquisition storage processing and display system using a computer controlled color coded display system developed by Adams and associates[8] The images were photographed separately as a series of 10 color coded isocount contours in spectral sequence The channel with the maximum counts was arbitrarily assigned the color red and each 10% change in counts resulted in a different color The scintigrams of the left and right coronary circulations appeared separately in combination and color Heparin (2 500 to 5 000 units) was given intra arterially at the beginning of the study and was reversed by protamine intravenously at the end of the procedure

Results

The patients were divided into four groups Groups A B and C were patients with angina pectoris—Group A patients with the ECG syndrome of septal fibrosis (Fig 1) Group B patients with the ECG syndrome of septal fibrosis and ECG changes of myocardial ischemia and/or infarction Group C patients with ECG changes of myocardial ischemia and/or infarction but *without* septal fibrosis Group D was composed of patients with chest pain but normal coronary arteries as shown by coronary arteriography Thirty patients were in Group A 35 in Group B 113 in Group C and 96 in Group D (Table I)

The age and sex distribution for Groups A B and C patients with angina pectoris is similar but a high percentage of females occurs in Group D patients The duration of angina pectoris is similar in patient Groups A B and C Of the 38

Table II Obstructive (≥ 70% narrowing) coronary lesions and the ECG syndrome of septal fibrosis

Groups (no)	Artery involvement						
		LAD					
	LAD	CIRCX	RC	CIRCX + RC	CIRCX	CIRCX + RC	RC
A (30)		8	2	10	0	1	2
B (35)	4	5	5	1	2	1	1
C (105)	15	22		45	6	3	7

Abbreviations no = number of patients LAD = left anterior descending artery CIRCX = circumflex artery RC = right coronary artery

exercise stressed patients with septal fibrosis (Groups A and B) 36 (96%) had positive responses as compared to 43 out of 68 (63%) for Group C patients

The number of arteries with a greater than 70% estimated cross sectional obstruction in Groups A B and C patients is given in Table II No differences are seen in the number of obstructed arteries relative to the number of patients in the three groups

Differences in the pathology of obstructive coronary arteries between the groups with (A and B) and without (C) septal fibrosis are seen in the frequency and severity of proximally located disease (Table III) Forty four (44) out of 65 patients (68%) with the ECG syndrome of septal fibrosis (Groups A and B) had obstructive lesions (≥70%) in the proximal LAD as compared to 48 out of 105 patients (45%) without the ECG syndrome a difference that is highly significant ($p < 0.001$) Considering the estimated atheromatous narrowing of the proximal LAD for all of the

Long-term benefit of dobutamine in patients with congestive cardiomyopathy

Donald V Unverferth M D *
Raymond D Magorien M D **
Richard P Lewis M D F A C C ***
Carl V Leier M D ****
Columbus Ohio

Dobutamine is a new synthetic catecholamine systematically formulated by Tuttle and Mills[1] Animal experiments demonstrated that this compound significantly increased ventricular contractility and cardiac output in a dose range which had little to no effect on heart rate and systemic blood pressure[2,3] Short and long term infusions of dobutamine in patients with cardiac failure also improved ventricular performance and increased cardiac output while decreasing left ventricular filling pressure and systemic vascular resistance these beneficial effects were achieved without a significant increase in afterload or heart rate [4] This laboratory previously reported that the mean cardiac index and left ventricular function parameters (echocardiograms and systolic time intervals) remained improved above baseline values 30 minutes after the discontinuation of a 72 hour dobutamine infusion (in patients with congestive cardiomyopathy and severe cardiac failure) symptomatic improvement [illegible]sisted up to one week post infusion in 68% of t[illegible] patients The purpose of this study is to de[illegible]mine whether prolonged infusion of dobuta[illegible] results in persistent symptomatic and or ob[illegible]tive improvement of cardiovascular functio[illegible] patients with low output cardiac failure

Methods

Patient population The 38 patients selected [illegible] the study had symptoms of severe left h[illegible] failure There were 29 men and nine women [illegible] age range was 17 to 73 years the mean a[illegible] 51 2 years The diagnosis of congestive ca[illegible]myopathy (COCM) was made by history p[illegible]cal examination and cardiac catheteriza[illegible] Patients who had a greater than 50% occlus[illegible] a coronary artery by angiography were excl[illegible] from the study Also excluded were patients [illegible] had consumed more than one drink of alcohol [illegible] day for the three months prior to study [illegible] etiology of the heart disease was commonly i[illegible]pathic (20 of 38 53%) but other factors were [illegible] important (Table I) Frequently two fac[illegible] such as alcohol and hypertension may h[illegible] contributed The protocol was approved by [illegible] Human Research Committee

This group of 38 patients can be further ch[illegible]acterized by their symptoms physical fi[illegible] electrocardiograms and hemodynamic data T[illegible] symptoms at time of study included dysp[illegible] [illegible] of 38 100%) peripheral edema (20 of 38 5[illegible] atypical chest pain (18 of 38 47%) easy fatig[illegible]bility (10 of 38 26%) palpitations (nine of [illegible] 24%) and abdominal swelling (nine of 3[illegible] [illegible] The most prominent physical findings [illegible]

From the Division of Cardiology Department of Medicine The Ohio State University Hospitals, Columbus, Ohio

Supported by a grant from the Central Ohio Heart Chapter of the American Heart Association

Received for publication Aug 23 1979

Accepted for publication [illegible] 1979

Reprint requests Donald V Unverferth, M D 65 Means Hall, Division of Cardiology Ohio State University Hospitals, 466 W Tenth Ave Columbus OH [illegible]

*Recipient of the Young Investigator Award of the Central Ohio Heart Association Assistant Professor [illegible] Medicine Division of Cardiology Ohio State University Hospital Dept of Medicine Columbus.

**Instructor of Medicine Division of Cardiology Ohio State University Hospitals.

***Professor of Medicine Division of Cardiology Ohio State University Hospitals.

****Assistant Professor of Medicine [illegible] Pharmacology Division of Cardiology Ohio State University Hospital.

0002-8703/80/110622 + 09$00 90/0 © 1980 The C [illegible]

Table IV Myocardial scintigrams and the ECG syndrome of septal fibrosis

Groups (no)	*Septum*				*Left ventricle*			
	Normal		*Abnormal*		*Normal*		*Abnormal*	
	No	%	*No*	%	*No*	%	*No*	%
A (28)	13	46	15	54	10	35	18	65
B (34)	12	35	22	65	8	23	26	77
C (84)	64	77	20	23	41	48	43	52
p	A + B vs. C – < 0 001				A + B vs C – < 0 05			

No = number of patients
Statistical probability Chi square test.

what might be considered a minor ECG abnormality the loss of Q wave from the initial depolarization through the ventricular septum

It may be more than coincidence that the 23% of patients without the ECG syndromes of septal fibrosis had abnormal septal scintigrams while Burch and De Pasquale[2] found a 20% incidence of histologically proven septal fibrosis in the 1 184 hearts with previous ECG evidence of normal septal depolarization A most likely explanation for this similarity is that septal fibrosis or infarctions in regions remote from the initial depolarization pathway do not affect the Q wave inscription in the ECG leads subtending the ventricular septum

The 96% positive exercise stress response the significantly higher incidence of proximally located obstructive lesions of the LAD (Table III) and the higher percentage of abnormal ventricular septal and left ventricular myocardial scintigrams (Table IV) coupled with the infrequency of the ECG syndrome of septal fibrosis in patients with nonobstructive coronary artery disease (4%) when viewed together provide compelling evidence that the ECG syndrome of septal fibrosis is a useful clue for identifying a subset of angina pectoris patients with advanced coronary artery disease of the proximal LAD and diffuse left ventricular hypoperfusion

Summary

Coronary artery disease (CAD) and myocardial perfusion were assessed by arteriograms and scintigrams (Technetium 99 microspheres alone or combined with Iodine 131 albumin macroaggregates) in 178 angina pectoris patients with and without the electrocardiographic (ECG) syndrome of septal fibrosis and with ≥70% obstruction in one or more coronary arteries The ECGs of 96 patients without angiographic evidence of obstructive CAD were also examined for the ECG syndrome of septal fibrosis Patients with the ECG syndrome of septal fibrosis have significantly higher incidences of positive exercise stress test of ≥70% narrowing of the proximal left anterior descending (LAD) artery of severe proximal LAD disease and of more extensive left ventricular hypoperfusion than patients without the ECG syndrome The fact that only 4% of patients without obstructive CAD have the ECG syndrome of septal fibrosis indicates the usefulness of the syndrome in identifying a subset of angina pectoris patients with advanced CAD of the proximal LAD and diffuse left ventricular hypoperfusion

The assistance of Mrs Heidi Fowler and Mrs Nan Blanchard in preparing the manuscript is gratefully recognized

REFERENCES

1 Burch G E An electrocardiographic syndrome characterized by absence of Q in Lead I aVL V and V Am Heart J 51 487 1956
2 Burch G E, and De Pasquale N A study at autopsy of the relation of absence of the Q wave in Leads I aV_L V and V to septal fibrosis Am Heart J 60 336 1960
3 Goldman M J Principles of clinical electrocardiography Los Altos Calif 1973 Lange Medical Publications p 131
4 Witham A C VCG patterns of myocardial scarring in the absence of diagnostic Q waves *in* Advances in electrocardiography New York 1972 Grune & Stratton, Inc p 349
5 Judkins M P Percutaneous transfemoral selective coronary arteriography Radiol Clin North Am 6 467 1968
6 Adams, R Braun E J, and Finney C Computer processing of image data with color coded isocount contour display J Nucl Med 11 380 1970
7 Jansen C Judkins M P, Grames, G M Gander M, and Adams, R Myocardial perfusion color scintigraphy with MAA Radiology 109 369 1973
8 Sodi Pallares D Rodriguez M I Chait L P and Zuckerman R The activation of the interventricular septum Am Heart J 41 569 1951
9 James T N, and Burch G E Blood supply of the human interventricular septum Circulation 17 391 1958

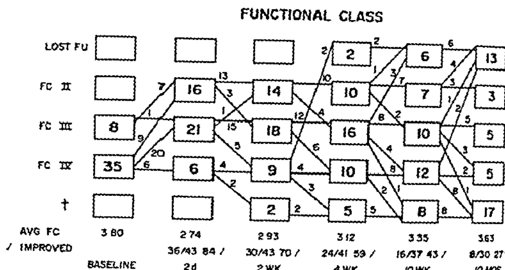


Fig 1 This graph details the number of patients in each functional class *(FC)* at each time period from baseline to 10 months after completion of the dobutamine infusion If we could not contact a patient he was considered lost to follow up *(Lost FU)* Those who died (†) were considered to be in *FC IV* for average FC determinations those lost to follow up were not included in average functional class determinations. Only those patients in a higher functional class compared to their baseline were considered improved for the percent improved of this graph.

functional class determination via telephone interviews

Results

The 38 patients received a total of 43 three day infusions of dobutamine five patients received the drug twice Every patient improved his cardiac function during the infusion as measured by the %ΔD and the PEP/LVET The average increase of %ΔD was 6 8% ± 0 7 ($\bar{x}$ ± SEM $p < 0\,001$) and the average decrease of the PEP/LVET was 0 16 ± 03 ($\bar{x}$ ± SEM $p < 0\,001$) Most patients continued to have subjective and objective evidence of improved left ventricular function after discontinuation of the drug

The improvement of functional class (FC) after dobutamine is shown in Fig 1 The average FC of all patients prior to dobutamine was 3 8 Two days after completion of dobutamine the average FC was 2 7 and at two weeks it was 2 9 Even at four and ten weeks the FC was 3 1 and 3 4 By 10 months however the average FC was 3 6 The number of patients improved decreased from 83% at two days and 70% at two weeks to just 27% at 10 months

Results of serial systolic time intervals are shown in Fig 2 The data were best organized over four time periods If a patient had more than one measurement during this interval the data were averaged Those patients studied maintained a significant ($p < 0\,001$) decrease of the PEP/LVET over pre drug control at all fou periods Similarly the echocardiographic % shown in Fig 3 This shows a signi ($p < 0\,05$) improvement at 2 3 days and impressive changes at 4 3 weeks and 9 9 and at 10 4 months ($p < 0\,01$)

Fig 4 details the results of the systolic intervals after discontinuation of dobutami the time when measurements were taken change from baseline is shown Improvemen considered significant if there was a one sta deviation (–0 04) change [9] This standard d tion was established by sequential studi patients with chronic myocardial disease T patients who died of congestive heart failure considered as having deteriorated in their tion tests However those who died of arr mias embolus or other causes were not enter this table Those test results that indica change of –0 04 are connected by a solid line indicate improvement A lesser change or a r the PEP/LVET is shown by a broken line At time period seven days after dobutamine 67% of 30) had an improved PEP/LVET At t months 52% (12 of 23) were better and even months 31% (five of 16) had evidence of impr left ventricular function

The change of %ΔD from baseline is show Fig 5 Improvement was considered significa there was a 2% rise in this measurement The rise was considered significant because in a F

gallop rhythm in all 38 patients 92% (35 of 38) had a left ventricular protodiastolic gallop and 74% (28 of 38) had a left ventricular presystolic gallop. Right ventricular protodiastolic (13 of 38, 34%) and presystolic (11 of 38, 32%) gallop sounds were also noted. The murmur of mitral regurgitation was present in 61% (23 of 38) and tricuspid regurgitation was observed in 16% (six of 38) of the patients. The electrocardiograms often showed conduction disease. There were 11 patients (11 of 38, 29%) with complete left bundle branch block and 16 (16 of 38, 42%) with left intraventricular conduction delay. Also 11 patients (11 of 38, 29%) had a left axis deviation and three (three of 38, 8%) had a right bundle branch block. Arrhythmias were frequently recorded. Seven patients (seven of 38, 18%) had atrial fibrillation and twelve (12 of 38, 32%) had frequent premature atrial or ventricular contractions. Findings at catheterization were consistent with severe left heart failure. The angiographic ejection fraction ranged from 0.09 to 0.42 with a mean of 0.25 ± .02 ($\bar{x}$ ± SEM) and the cardiac index ranged from 1.5 to 2.9 liters/min/M² ($\bar{x}$ = 2.0 ± 0.1). The pulmonary wedge pressure averaged 23.4 mm Hg ($\bar{x}$ = 23.4 ± 1.9).

Infusion period and studies. Written informed consent was obtained from each patient. Dobutamine was delivered intravenously with a calibrated Harvard pump for 72 hours. Dobutamine was started at 2.5 mcg/kg/minute and was increased every 30 minutes in 2.5 mcg/kg/minute dose increments up to a maximal dose of 15 mcg/kg/minute. The maintenance dose for each patient was determined on the basis of data derived from the dose response phase and had to meet the following criteria: heart rate increase of < 120% of control, systolic blood pressure < 120% of control, pulmonary capillary wedge pressure < 140% of control, and premature ventricular contraction of < 12/minute. After six hours of the maintenance dose and daily thereafter, the dose was re-evaluated for each patient and was increased or decreased based on the criteria noted above.

The electrocardiogram was monitored continuously over the 24 hours prior to the infusion period and continually during the infusion. An echocardiogram and systolic time interval determinations were performed 30 minutes before the infusion began, daily during the infusion period and at intervals as discussed below. Systolic time intervals were obtained with an Electronics for Medicine VR6 or with a Smith Kline French Echoline 20 unit utilizing the specifications previously outlined.[9] The PEP/LVET was used as the measure of left ventricular performance. Echocardiograms were performed with a Unirad series C echoscope and an Electronics for Medicine VR6 recorder or an Irex echoscope with the SKF Echoline 20 recorder. The %ΔD was used as the echocardiographic determinant of left ventricular function and was derived from the formula:

Table I. Contributing factors to heart failure (38 patients)

Idiopathic	20 patients	53%
Alcohol	17 patients	45%
Hypertension	10 patients	26%
Possible viral disease	4 patients	11%
Peripartum	3 patients	8%
Diabetes	2 patients	5%
Amyloidosis	2 patients	5%

$$\%\Delta D = \frac{\textit{end diastolic diameter} - \text{end systolic diameter}}{\text{end diastolic diameter}} \times 100$$

The left ventricular free wall thickness and end diastolic diameter were measured at end-diastole prior to dobutamine infusion.

Follow-up information. Patients were contacted and were encouraged to return to the medical center for an interview, physical examination, and non-invasive measurement of left ventricular function. The functional class determinations were made by two of the investigators (D.V.U. and C.V.L.). Patients were considered lost to follow-up for functional class determination if we were unable to contact them or if they were started on additional drug therapy. Initiation of additional drug therapy was not necessarily a sign of dobutamine failure because many patients were placed in other studies after several months. Patients who died were considered to be in the unimproved functional category despite the fact that several patients had objective and subjective signs of improvement but died of an embolus or a dysrhythmia. Digitalis and diuretics were maintained at the same dosage level throughout the study. Vasodilators were not prescribed. Patients who were unable to travel were excluded from the non-invasive measurement portion of this study but were included in the

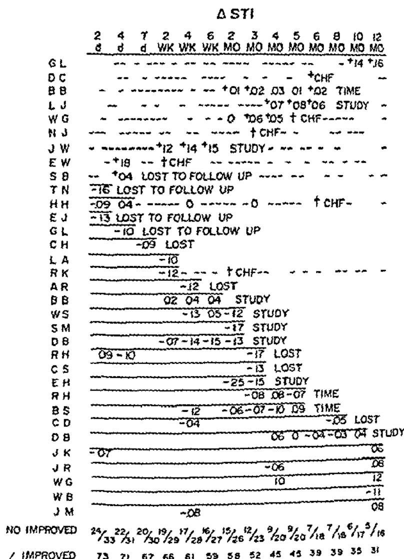


Fig 4 The change of each patient s PEP/LVET from baseline are shown Those who died (†) and the cause of death (*CHF* = congestive heart failure) are noted The study was completed while some patients were under observation (*Time*) some patients were placed on another study (*Study*) and some could not travel to the medical center for examination (*Lost* = lost to follow up) Those who had an improvement of less than –0 04 or who had a worsening of the ratio or who died are noted by a *dashed line* linking their initials to their data Those patients who had an improvement of greater than –0 04 of the PEP/LVET have a *solid line* linking their initials and running above their data Those who died or did not improve were considered to be unimproved for all 12 months of the study Those who improved the PEP/LVET were considered to be improved only for the time of observation The percent improved at each time period after dobutamine is shown at the bottom of the graph

diograms 22 (58%) had a decrease of their left ventricular diameter

The average survival of these patients from the onset of symptoms was approximately nine years and is illustrated in Fig 6 No patient has survived more than 20 years from the onset of symptoms The cause of death in the 17 patients who died during the time of the study was pulmonary embolus (six of 17 35%) intractable left heart failure (six of 17 35%) ventricular arrhythmias (four of 17 23%) and sepsis (… 17 6%)

Discussion

Therapy of congestive cardiomyopathy ha… ditionally been digitalis and diuretics Ther… a wave of popularity for extended bed rest i… 1960 s and the early 1970 s … This treat… decreased heart size in those with alcoh… peripartal … or idiopathic cardiomyop…

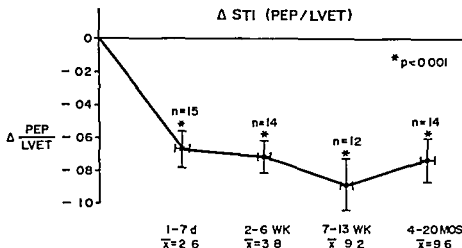


Fig 2 The change of the PEP/LVET of the systolic time intervals from baseline is shown at four time periods after dobutamine infusion The number of patients measured at each period is shown Some patients had two or more measurements made during a time period and these were averaged. *Brackets* represent the standard error of the mean

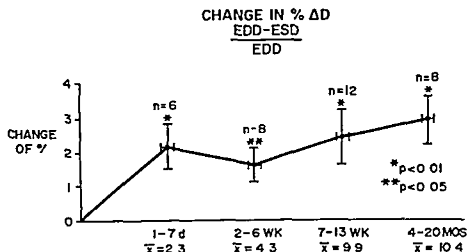


Fig 3 The change of the echocardiographic %ΔD from baseline at four time periods after dobutamine infusion is shown The number of patients measured during each period is shown Some patients had two or more measurements during a time period these values were averaged *The brackets* represent the standard error of the mean

of 15 patients with stable heart failure the one standard deviation of serial %ΔD measurements of the echocardiograms was 1 7% At one week after discontinuation of dobutamine 60% (18 of 30) had an improved %ΔD At two and six weeks 55% (16 of 29) and 50% (14 of 28) were still improved At three six and 12 months 48% (13 of 27) 42% (10 of 24) and 22% (four of 18) had a %ΔD at least 2% better than control

The left ventricular wall thickness (LVWT) had some prognostic implications Those patients who had symptomatic improvement had a thicker left ventricular free wall (corrected for body surface area) 0 59 cm/M² ± 03 (x̄ ± SEM) compared to those who did not improve 0 53 cm/M ± 04 Also only 24% (seven of 29) of those who improved had LVWT less than 0 5 cm/M while 56% (five of nine) of those who did not improve had LVWT less than 0.5 cm/M²

The left ventricular end diastolic diameter decreased slightly from an average pre dobutamine value of 6 58 ± 17 cm (x̄ ± SEM) to a post dobutamine diameter of 6 45 ± 14 ($p < 0.05$) Of the 38 patients who had echocar

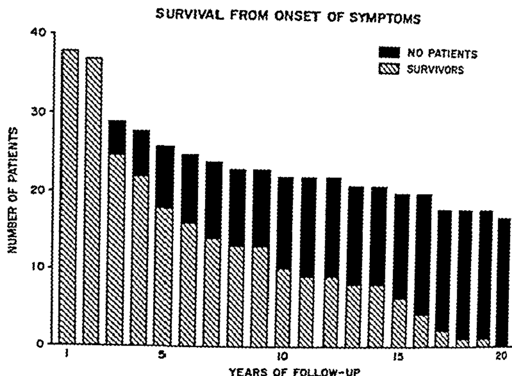


Fig 6 This graph demonstrates the survival of our 38 patients from the onset of symptoms The total number of patients is shown by the *height* of the bars Those who are still living at each year are illustrated by the *cross hatched portion* of the bars while those who have died are shown by the *solid portions* of the bars

ogy of the particular patient s heart failure before institution of veno or arteriolar dilators [2,29] Caution has been urged in the use of nitrates hydralazine and prazosin because of both pharmacologic effects and adverse reactions [29] Because of the potential adverse effects of vasodilators and because not all patients improve with vasodilators consideration should be given to inotropic agents in the treatment of congestive cardiomyopathy

This study demonstrated that dobutamine induced an improvement of myocardial function both during the three day infusion and in the follow up period Most of the patients (84%) had symptomatic improvement two days after infusion 59% continued to feel better at four weeks and 43% continued to feel better at ten weeks (Fig 1) This improvement was documented by non invasive testing The PEP/LEVT was significantly improved at three days four and 10 weeks and at 10 months (Fig 2) The echocardiographic %ΔD was similarly significantly improved (Fig 3) in those patients whom we could recall for testing The number of patients improved at each time period is similar for the two tests with approximately 50% still maintaining improvement at three months Even at six months, [illegible] and 42% were improved by PEP/LVET and the %ΔD

There was a small (1 4 mm ± 0 7 (p < 0.0[illegible]) but significant decrease of end diastolic diameter by echocardiogram after the three day infusion The patients who had a functional class improvement usually had a thicker left ventricular free wall (greater than 0 5 cm /M [2]) than those who did not respond This is consistent with Hamby's study [3] He found that the patients with thicker left ventricular walls had a better prognosis than those with a thin wall

The mechanism of the prolonged improvement of COCM patients after a three day infusion of dobutamine is not understood The downward spiral of a decreasing cardiac output increasing peripheral vasoconstriction and fluid retention may be corrected during the infusion period The reversal of this spiral may enable the ventricle to assume a new level of function with a reduced peripheral resistance Another possible mechanism for prolonged functional improvement may be related to increased coronary artery flow Dobutamine not only increases cardiac output but also by [illegible] of its beta −1 action dilates coronary arteries

ECHO % ΔD CHANGE FROM BASELINE

	2 d	4 d	7 d	2 WK	3 WK	4 WK	6 WK	2 MO	3 MO	4 MO	5 MO	6 MO	8 MO	10 MO	12 MO
NO IMPROVED	22/31	21/30	18/30	16/29	16/29	16/29	14/28	14/28	13/27	12/26	12/26	10/24	7/21	5/19	4/18
% IMPROVED	71	70	60	55	55	55	50	50	48	46	46	42	33	26	22

Fig. 5. The change of each patient's echocardiographic % ΔD from baseline is illustrated. Those who died (†) and the cause of death (*CHF* = congestive heart failure) are noted. The study was completed while some patients were under observation *(Time)*, some patients were placed on another study *(Study)*, and some could not come to the medical center for further examination *(lost to FU)*. The patient's initials are connected to their data by a *dashed line* if the improvement was less than 2% or if the patient died (CHF). The initials are linked by a *solid line* that runs over the data if there was a 2% or greater improvement of the % ΔD. The percent improved at each time period is shown at the bottom of the graph.

and improvement was maintained for months in some of these patients.' This treatment has not had a great deal of popularity in recent years, however, because of the practical problems of maintaining strict bed rest. Also some investigators have found that in certain types of heart disease such as peripartal cardiomyopathy, heart size may return to normal without extended bed rest.' A compromise of a subdued life style is usually prescribed.

Acute alcohol intake alters myocardial mitochondrial and sarcoplasmic reticulum morphology, and chronic alcohol abuse leads to permanent destruction of myofibers with interstitial scarring. Thus the treatment of cardiomyopathic patients must include the avoidance of all alcohol. Discontinuation of alcohol after chronic abuse is associated with a gradual improvement of myocardial function over an eight week period. Before crediting any therapy with improvement of the status of patients with alcoholic cardiomyopathy, one must be sure that no alcohol has been consumed for at least two months.

Vasodilator therapy for heart failure is presently enjoying popularity. Several investigators have recommended consideration of the physiol

15 Demakis J G and Rahimtoola S H Peripartum cardiomyopathy Circulation 44 964 1971
16 Seftel H and Susser M Maternity and myocardial failure in African women Br Heart J 23 43 1961
17 Klein H and Harmjanz D Effect of ethanol infusion on the ultrastructure of human myocardium Postgrad Med J 51 325 1975
18 Alexander C S Idiopathic heart disease 1 Analysis of 100 cases with special reference to chronic alcoholism Am J Med 41 213 1966
19 Hibbs R G Ferrans V J Black W C Weilbacher D G Walsh J J and Burch G E Alcoholic cardiomyopathy an electron microscopic study AM HEART J 69 766 1965
20 Bulloch R T Pearce M B Murphy M L Jenkins B J and Davis J L Myocardial lesions in idiopathic and alcoholic cardiomyopathy Am J Cardiol 29 15 1972
21 Weishar R Sarma J S M Maruyama Y Fischer R Bertuglia S and Bing R J Reversibility of mitochondrial and contractile changes in the myocardium after cessation of prolonged ethanol intake Am J Cardiol 40 506 1977
22 Braunwald E Vasodilator therapy—a physiologic approach to the treatment of heart failure N Engl J Med 297 331 1977
23 Forrester J S and Waters D D Hospital treatment of congestive heart failure Management according to hemodynamic profile Am J Med 65 173 1978
24 Cohn J N and Franciosa J A Vasodilator therapy of cardiac failure N Engl J Med 297 254 1977
25 Mason D T Afterload reduction and cardiac performance Physiologic basis of systemic vasodilators as a new approach in treatment of congestive heart failure Am J Med 65 106 1978
26 Williams D O Bommer W J Miller R R Amsterdam E A and Mason D T Hemodynamic assessment of oral peripheral vasodilator therapy in chronic congestive heart failure prolonged effectiveness of isosorbide dinitrate Am J Cardiol 39 84 1977
27 Chatterjee K Massie B Rubin S Gelberg H Brundage B H and Ports T A Long term outpatient vasodilator therapy of congestive heart failure Consideration of agents at rest and during exercise Am J Med 65 134 1978
28 Franciosa J A and Cohn J N Hemodynamic responsiveness to short and long acting vasodilators in left ventricular failure Am J Med 65 126 1978
29 Packer M and Meller J Oral vasodilator therapy for chronic heart failure a plea for caution Am J Cardiol 42 686 1978
30 Mason D T Symposium perspective Am J Med 65 101 1978
31 Bleifeld W Kupper W Hanrath P and Mathey D New and traditional therapy of congestive heart failure A European view Am J Med 65 203 1978
32 Hamby R I Primary myocardial disease A prospective clinical and hemodynamic evaluation in 100 patients Medicine 49 55 1970
33 Baron G D Speden R N and Bohr D F Beta adrenergic receptors in coronary and skeletal muscle arteries Am J Physiol 223 878 1972
34 De La Lande I S Harvey J A and Holt S Response of the rabbit coronary arteries to autonomic agents Blood Vessels 11 319 1974

The increased coronary blood flow may enable some borderline ischemic regions of the subendocardium to repair hypoxic damage The salvage of such areas may improve ventricular performance These possibilities are currently being investigated

The weakness of our study is the absence of patient controls Because of the heterogeneity of COCM a controlled study would have to be very large to match etiologies age ventricular function and pressures Nevertheless a study should be performed in which patients would be randomized to control (digitalis and diuretics would be used in all groups) vasodilator therapy inotropic therapy and combined vasodilators and inotropes Such a study could recognize which patients benefit from each type of therapy in symptoms function and longevity

The therapy of congestive heart failure is expanding and dobutamine would appear to have a significant role Whether the therapy should be a single three day infusion intermittent or even continous infusions is undecided Finally an oral inotrope with properties similar to dobutamine would be of great value in the drug regimen of COCM

Summary

Dobutamine was given intravenously for three days to 38 patients with congestive cardiomyopathy The patients were followed by serial determinations of functional class and by non invasive measurements of left ventricular function systolic time intervals (PEP/LVET) and echocardiogram (%ΔD) The average functional class (FC) of this group was 3 8 prior to dobutamine but two days after completion the average FC was 2 7 by four weeks the average FC was 3 1 and by 10 weeks it was 3 4

The average PEP/LVET declined significantly ($p < 0\,001$) at three days four and nine weeks and at 10 months after the discontinuation of dobutamine infusion Also 67% (20 of 30) of patients had improvement of the PEP/LVET by greater than −0 04 at seven days Even two and six months after dobutamine 58% (15 of 26) and 39% (seven of 18) were improved Similarly the %ΔD was improved by at least 2% in 60% (18 of 30) at seven days and 55% (16 of 29) at four weeks At two and six months 50% (14 of 28) and 42% (10 of 24) were improved Those patients who did not improve their FC were more likely (five of nine) to have left ventricular free wall thickness (by echocardiogram) less than 0.5 cm /M Those who responded usually (22 of 29) had a ventricular wall thickness greater than 0.5 cm /M Although the mechanism of the prolonged improvement after a three day infusion of dobutamine is not understood this study suggests that dobutamine has a role in the therapy of chronic congestive heart failure

We would like to thank Patricia Huss R N, and Jackie Miller R N for the performance and measurement of the systolic time intervals and echocardiograms We would also like to thank Tami Griffith for the preparation of the manuscript

REFERENCES

1 Tuttle R. R and Mills J Derives de la dopamine Belgium patent No 89 051 1973.
2 Tuttle R R and Mills J Dobutamine development of a new catecholamine to selectively increase cardiac contractility Circ Res. 36 185 1975
3. Kraft Hunter F., and Hinds J E. Cardiac dynamic effects of increasing myocardial contractility without changing heart rate mean aortic pressures and end diastolic volume in conscious instrumented dogs (Abstr) Fed Proc 32 343 19 3
4 Vatner S F McRitchie R J and Braunwald E Effects of Dobutamine on left ventricular performance coronary dynamics and distribution of cardiac output in conscious dogs, J Clin Invest 53 1765 1974
5 Robie N W Nutter D O Moody C., and McNay J L. In vivo analysis of adrenergic receptor activity of Dobutamine Circ Res 84 663 19 4
6 Jewitt D Birkhead J., Mitchell, A and Dollery C Clinical cardiovascular pharmacology of dobutamine Lancet 2 263 1974
7 Beregovich, J Bianchi, C D Angelo R Diaz, R and Rubler S Hemodynamic effects of a new inotropic agent (dobutamine) in chronic cardiac failure Br Heart J 37 679 1975
8 Akhtar N Mikulic E Cohn J N., and Chaudhry M H Hemodynamic effects of dobutamine in patients with severe heart failure Am J Cardiol 36 202 1975
9 Leier C V Webel J and Bush C A The cardiovascular effects of the continous infusion of dobutamine in patients with severe heart failure Circulation 56 468 1977
10 Lewis R P Leighton R F Forester W F and Weissler A. M Systolic Time Intervals in Non Invasive Cardiology Weissler A M ed New York, 1974 Crane & Stratton, Inc p 301
11 McDonald, C D Burch G E., and Walsh, J J Alcoholic cardiomyopathy managed with prolonged bed rest Ann Intern Med 74 681 1971
12 Burch G E McDonald C D and Walsh J J The effect of prolonged bed rest on postpartal cardiomyopathy AM HEART J 81 186 1971
13 Walsh J J Burch G E Black W G Ferrans V J and Hibbs R G Idiopathic myocardiopathy of the puerperium (postpartal heart disease) Circulation 32 19 1965
14 Burch, G E. Walsh J J and Black W C Value of prolonged bed rest in management of cardiomyopathy J.A M.A 183 81 1963

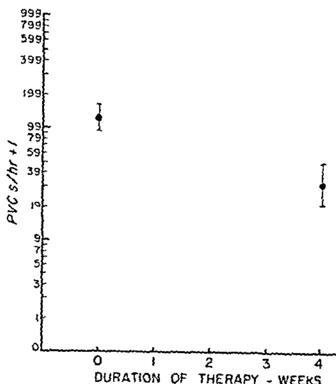


Fig 1 An illustration of the results of short term (4 weeks) acebutolol therapy on the incidence of PVCs Standard error of the mean is used in all instances

weeks of therapy all patients had a second chest x ray and repeat opthalmological testing All 20 patients had serum levels of acebutolol and its active acetyl metabolite measured approximately two to four hours after the last dose of the drug according to the method of Meffin and associates[4] The serum drug level estimations coincided with the day of the four week Holter recording

At the time of entry into the study 14 of 20 patients had a prior history of myocardial infarction with stable angina pectoris Two patients with a prior history of myocardial infarction had no post infarction angina All patients with prior myocardial infarction were at least three months post myocardial infarction at the time of the study entry Four patients with no history of prior myocardial infarction had stable angina None of the patients had unstable angina at the time of study entry Five patients had had saphenous vein bypass surgery performed at least one year prior to study entry for angina pectoris resistant to conservative medical management All 20 patients were in New York Heart Association Functional Class I or II without clinical evidence of congestive heart failure However four of 20 patients had on baseline chest x ray a cardiothoracic ratio of greater than 50% All 20 patients had normal renal and hepatic functi[illegible] No patient had a positive ANA titer prior t[illegible] study entry

On baseline electrocardiogram remote transmural myocardial infarction was present in e[illegible] of the 20 patients In the remaining 1[illegible] patients the electrocardiogram was either normal or revealed only nonspecific ST T changes One patient had complete right bundle branch block No A V block or resting heart rates of less than [illegible] beats per minute were observed in any of the patients

At the time of entry into the study seven of [illegible] patients had no symptoms suggestive of card[illegible] arrhythmia and were selected for the study on the basis of frequent premature ventricular contractions noted on 12 lead electrocardiograms d[illegible] during routine clinic visits One patient had s[illegible] copal spells unrelated to postural change me[illegible] bolic abnormality or neurological disease Twelve patients had unexplained d[illegible] spells with or without palpitations

The 24 hour Holter tapes were analyzed us[illegible] the Model 660 A Avionics electrocardiosc[illegible] and the following features were quantitated (1) the number of PVCs expressed as the number per hour (2) the number of episodes of paired PVCs and (3) the number of episodes of PVCs in r[illegible] of three or more For the purposes of this study three or more consecutive PVCs at a rate in excess of 120 beats per minute were considered to represent ventricular tachycardia Similar runs [illegible] rates between 60 and 120 beats per minute were considered to represent accelerated idioventricular rhythm The Model 660 A Avionics electroca[illegible] dioscanner allowed playback of the tapes [illegible] speeds of 1 30 60 and 120 times real time. T[illegible] detect and quantitate ventricular arrhythmias [illegible] used oscilloscopic display of one or two simul[illegible] neous channels of electrocardiographic leads [illegible] the R R interval and an R wave triggered [illegible] system and the Avionics arrhythmia analyzer The arrhythmia analyzer employed variabl[illegible] characteristics of prematurity QRS width, and amplitude to detect and quantitate ventricular ect[illegible] ectopy The frequency of ventricular [illegible] beats expressed as the number per hour [illegible] displayed on the scanner and a trend pr[illegible] record showed the hourly count of ventric[illegible] ectopic beats In addition all tapes were man[illegible] ly scanned and all areas of questionable accura[illegible] were verified by direct writeout and hand re[illegible] ing with evaluation of these rhythm strips [illegible]

The long-term suppression of ventricular arrhythmia by oral acebutolol in patients with coronary artery disease*

Neil de Soyza M B B S
James J Kane M D
Marvin L Murphy M D
Atul R Laddu M D
James E Doherty M D
Joe K Bissett M D
Little Rock Ark

Beta blocking agents have enjoyed increasing popularity in managing post myocardial infarction patients since long term prophylactic administration of beta blocking agents to survivors of myocardial infarction has been shown to result in a decreased incidence of sudden death Many beta blocking agents with claims for less effects than propranolol on noncardiac beta receptors are currently undergoing clinical evaluation Acebutolol [(±) 1 (2 acetyle 4 butyramido phenoxy) 3 isopropylamino propan 2 ol hydrochloride] a relatively cardioselective adrenergic receptor blocking drug with weak sympathomimetic activity is one such drug Even though its efficacy when used both parenterally and orally in treating ventricular ectopy over a short period has been shown in several studies the long term efficacy and safety of oral acebutolol has not been well documented

Material and Methods

Patients for this study were selected on the basis of the presence of a minimum of 10 PVCs per hour (mean) present on a single 24 hour Holter monitor performed after discontinuing digitalis and antiarrhythmic drugs for at least one week During the entire study period patients continued to remain without concurrent therapy with digitalis preparation or other antiarrhythmic drugs Only patients with documented coronary artery disease were eligible for selection for the study Patients with congestive heart failure symptomatic chronic obstructive lung disease insulin dependent diabetes and significant opthalmological disease were also excluded Due to untoward effects noted with other beta blocking agents on the eye all patients being considered for the study had detailed opthalmological testing by an opthalmologist and any patient with a significant opthalmological problem was excluded

After obtaining informed consent 20 male patients with an average age of 57 years and a minimum of 10 PVCs per hour (mean) on baseline Holter monitoring had complete physical examination chest x ray 12 lead electrocardiogram and laboratory tests including an antinuclear antibody (ANA) titer performed at baseline Oral acebutolol was then commenced at a dose of 100 mg orally every eight hours and was continued for fours weeks During this period weekly 24 hour Holter monitoring was performed using a two channel Avionics Model 445 electrocardiocorder The daily dose and the frequency of acebutolol were adjusted depending on the effect of the drug on the PVC frequency noted during weekly Holter monitoring At the end of four

From the V te ns Administration Medical Center Dep rtm nt of Medicine nd Uni rsity of Arkansas f Medic l Sciences C mpus Little Rock.

Received f p blic tion N 7 19 9
Accepted f public t on Dec 14 1979

Reprint req ests N l de Soyza M B B S Directo Coron ry Care Unit (111B) V terans Administrat n Med cal Ce te 300 E. Roosevelt Rd Littl Rock, A k. 72206

*This pape was presented in part at the An ual Sc t fic Sessio of the American College of Cardi l gy at Miami, Fl rida, in M rch 1979

000?-8 03/80/110631 + 08$00 80/0 © 1980 The C V Mosby Co

Table I Results of acebutolol therapy on PVC incidence

	Short term trial							
	Control			4 weeks				
Pt no	PVC/hr	PVC pairs	PVT	PVC/hr	PVC pairs	PVT	Dose	Side ef
1	14	–	–	1	–	–	600	–
2	996	42	2	162	14	–	1,200	–
3	86	1	–	20	–	–	800	GI Int
4	101	–	–	11	–	–	1,200	–
5	50	–	–	7	–	1	900	GI Int
6	57	2	–	15	–	–	900	–
7	53	–	–	0	–	–	900	–
8	1 797	86	–	275	–	–	1,200	GI I
9	119	–	–	1	–	–	1,200	–
10	651	26	–	8	–	–	1,200	–
11	158	–	–	1	–	–	1,200	–
12	477	44	1	529	32	–	1 600	CHF
13	24	–	–	13	–	–	300	–
14	179	–	–	369	–	–	1,200	–
15	110	31	–	97	36	1	1,200	Mild C
16	187	1	–	190	2	–	1,200	–
17	75	–	–	186	–	–	1,200	–
18	100	–	–	67	1	–	1,200	–
19	131	6	–	181	9	–	1,200	–
20	66	6	–	163	23	–	900	–

Abbreviations CHF = congestive heart failure GI Intol = gastrointestinal intolerance PVC = premature ventricular contraction PVT … of episodes of paroxysmal ventricular tachycardia

therapy to a geometric mean number of 32 PVCs per hour ($P < 0.005$) However when the responses of the individual patients were considered PVC reduction from baseline values was greater than 90% in four patients and greater than 70% in 11 of 20 patients In the remaining nine patients PVC reduction from baseline values was less than 50% in fact in six of these nine poorly responding patients there was no reduction in PVCs from baseline values (Table I)

In six patients with paired PVCs at baseline paired PVCs were noted after four weeks of acebutolol therapy in four patients (Table I) Three of these four patients were non responders (patients showing less than 70% total PVC reduction) Even though the two patients with baseline PVT had no PVT following therapy two other patients without PVT at baseline had one three beat episode each of PVT after four weeks of acebutolol therapy Again one of these two latter patients was a non responder

In all 20 patients the mean serum level of acebutolol was 759 ± 353 (standard deviation) ng/ml The corresponding serum level of its acetyl metabolite was 1 756 ± 797 (SD) ng/ml giving a metabolite to unchanged acebutolol of 2 3 1 The mean serum levels of acebutolo… its metabolite in the 11 patients responding… greater than 70% PVC reduction 723 ± 29… ng/ml and 1 807 783 (SD) ng/ml respect… were not significantly different from the … sponding serum levels in the nine rema… non responders 796 ± 411 (SD) ng/ml… acebutolol and 1 705 ± 811 (SD) ng/ml f… acetyl metabolite

No syncope or near syncope was noted d… therapy in any patient All 11 patients respo… with greater than 70% total PVC redu… remained free or became free of symptoms s… tive of cardiac arrhythmia after therapy H… er since only highly subjective symptoms … palpitations and dizzy spells were noted in … of our patients the effect of acebutolol th… on symptoms suggestive of arrhythmia can… adequately evaluated from the present stud…

The mean resting heart rate at baseline in … patients was 77 beats per minute and af… weeks of therapy 63 beats per … ($P < 0.001$) The mean heart rate before and… acebutolol therapy in the 11 "responders…

cardiologist During analysis of the data the term complex PVCs was used to mean an arrhythmia with two or more of the following features during the 24 hour Holter monitoring greater than 10 PVCs per hour paired PVCs and paroxysmal ventricular tachycardia (PVT)

These data were analyzed by use of Student s t test In comparing means across time the paired t test was used In comparing groups of responders versus non responders the unpaired t test was applied For the PVC data a variance stabilizing transformation was applied to the data before analysis by the t test This transformation amounted to adding the number one to each PVC count and then taking the natural logarithm (essentially this amounts to testing for significant differences among geometric rather than arithmetic means)

During the four weeks of therapy acebutolol was administered on a thrice daily schedule in 12 of the 20 patients and on a four times daily schedule in the remaining eight patients The average daily dose of acebutolol used in the 20 patients during the four week trial was 1 100 mg (range 600 to 1 600 mg)

In order to determine the long term efficacy and safety of the drug nine of the 11 patients responding with greater than 70% PVC reduction from baseline values during the four weeks of acebutolol therapy who consented to join the long term evaluation were continued on acebutolol for 12 months The two patients who did show a satisfactory response at the conclusion of the short term study who were excluded from the long term study were one patient who left the state of Arkansas and was not available for long term participation and a second who decided not to participate in a long term study for personal reasons During the 12 months of therapy all patients returned for 12 lead electrocardiograms and physical examinations every four weeks At the 1 month 4 month 8 month and 12 month visits all patients in addition had 24 hour Holter monitoring chest x ray laboratory tests including an ANA titer and detailed opthalmological testing During the long term evaluation the acebutolol dosage and frequency were adjusted depending on the clinical response and the frequency of ventricular ectopics as noted on the serial 24 hour Holter monitor recordings

The average daily dose of acebutolol used in the long term trial was 1 300 mg (range 600 to 1 600 mg per day) The acebutolol was administered on

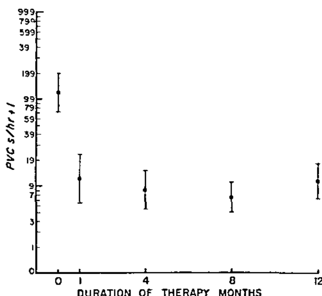


Fig 2 An illustration of the response of long term acebutolol therapy 0 = PVC incidence at baseline (pre drug) Standard error of the mean is used in all instances

a thrice daily basis in three of the nine patients and on a four times daily schedule in the remaining six patients The characteristics of the nine patients on the long term trial were as follows (1) average age 56 years (2) all had stable angina pectoris (3) six of nine patients had had prior myocardial infarction not less than three months prior to study entry and (4) four of nine patients had had prior saphenous vein bypass surgery at least one year prior to study entry

Of the nine long term subjects three were free of symptoms suggestive of cardiac arrhythmia at baseline Six patients has unexplained dizzy spells with or without palpitations prior to starting acebutolol therapy None of the long term study patients gave a prior history of syncope or cardiac arrest

The Holter recordings performed on the long term evaluation were analyzed in the same way that the short term Holter recordings were analyzed and the same arrhythmia characteristics were quantitated

Results

Short term trial (four weeks of therapy) The results of short term acebutolol administration in the 20 patients studied are shown in Fig 1 When the response to therapy of the whole study group was considered the geometric mean number of PVCs per hour in the 20 patients before therapy (125) was significantly lowered by acebutolol

Table II Complex PVCs during therapy in all nine patients

	>10 PVCs/hr	Paired PVCs	PVT
Baseline	9 pts	5 pts.	1 pt
12 month visit	5 pts	2 pts	0 pts.
At least once during therapy	8 pts	4 pts.	2 pts

PVC = premature ventricular contraction PVT = number of episodes of paroxysmal ventricular tachycardia.

nificant fluctuations in PVC counts once therapy was commenced

Prior to acebutolol therapy the geometric mean number of PVCs per hour in the nine study patients was 117 and at the 12 month visit the geometric mean number of PVCs per hour was 11 ($P < 0.001$) The geometric mean number of PVCs noted at the 1 month 4 month 8 month and 12 month Holter recordings was nine per hour and was not significantly different from the geometric mean number of PVCs at the 12 month visit (11 per hour)

After 12 months of acebutolol therapy the percentage reduction in PVCs noted at the 12 month visit was greater than 90% in four of nine patients greater than 80% in six patients and greater than 60% in seven patients One patient had a 46% reduction in PVCs and one patient had no reduction in PVCs at the 12 month visit This patient who did not respond to long term acebutolol therapy who also happened to have the smallest number of baseline PVCs (14 per hour) had excellent PVC control through eight months of therapy and showed a sudden unexplained increase in PVCs to 58 per hour at the 12 month visit (Table I)

Even though over all decrease in PVCs was impressive complex features of ventricular ectopy persisted despite acebutolol therapy in some patients This is shown in Table II in which it can be seen that greater than 10 PVCs per hour and paired PVCs persisted during therapy in some patients Paired PVCs present at baseline in five patients were abolished on the four Holter recordings during therapy in only two patients PVT was abolished in the one patient having PVT at baseline However in two other patients PVT was noted during therapy Each of these two patients had one three beat episode of PVT each on a single Holter recording done during therapy One of these patients also had one episode of accelerated idioventricular rhythm during therapy However all patients remained symptom[...] in spite of these observations

As was observed during the short term t[...] the blood pressure and the PR QRS a[...] intervals on the 12 lead ECGs were not si[...]cantly changed before and during long term [...]butolol therapy Significant beta blockade [...] apparent even during long term therapy by [...] fact that the mean resting heart rate fell fr[...] baseline mean value of 79 beats per minute in [...] nine patients to 62 beats per minute afte[...] months of acebutolol therapy No symptom[...] bradyarrhythmias were encountered during [...] long term trial. During long term therapy [...] ocular or hematological side effects [...] observed

Discussion

Previous studies using acebutolol both or[...] and parenterally have shown that acebutol[...] both safe and effective over a short perio[...] patients with PVCs[3] The present study sh[...] that in the small number of patients studied[...] initial therapeutic response can be expected t[...] maintained over the long term in the majori[...] patients with safety In nine of the 11 pati[...] satisfactorily responding to the four week tri[...] acebutolol and who consented to participat[...] the long term acebutolol trial for 12 month[...] greater than 80% PVC reduction was mainta[...] through one year of therapy in two-thirds of t[...] patients Recent cardiovascular literature [...] focused on the limitations of 24 hour electro[...]diographic monitoring in evaluating the effic[...] of antiarrhythmic agents mainly due to d[...] to-day variability of PVC incidence in pati[...] with cardiac arrhythmia[7] Using two 24-h[...] Holter recordings an approximately 80% P[...] reduction from baseline values is thought to [...] sufficient statistically for establishing therape[...] efficacy in antiarrhythmic drug evaluatio[...] Thus using these stringent criteria it can be s[...] that in the majority of the patients in the pres[...] study long term acebutolol therapy did main[...] a greater than 80% PVC reduction through t[...] initial 12 months of therapy

This study also shows that of the nine of[...] patients who failed to respond to acebu[...] therapy satisfactorily six patients had an ac[...] increase in PVCs following acebutolol thera[...] An excellent response or no response with re[...] to antiarrhythmic efficacy has been sugges[...] previously with propranolol therapy Our re[...]

Long term trial										
4 mo			8 month			12 month				
PVC/hr	PVC pairs	PVT	PVC/hr	PVC pairs	PVT	PVC/hr	PVC pairs	PVT	Dose	Side effects
5	–	–	1	–	–	58	–	–	600	–
23	–	–	5	–	–	56	3	–	1,200	–
46	–	–	40	–	–	33	–	–	600	–
73	–	–	5	–	–	1	1	–	1,200	–
29	–	–	17	–	–	2	–	–	1,200	Alopecia
7	–	–	11	2	–	8	3	–	1 600	Impotence
1	–	–	1	–	–	1	–	–	900	–
1	–	–	1	–	–	1	–	–	1 600	–
0	–	–	34	4	–	11	–	–	1 600	–

tients showing greater than 70% PVC reduction) was 80 beats per minute and 63 beats per minute respectively (P < 0 001) and in the nine non responders it was 73 and 63 beats per minute respectively (P < 0 001) However the difference in the bradycardic response following acebutolol therapy between the 11 responders and the nine non responders was not statistically significant

The mean systolic blood pressure before and after four weeks of acebutolol therapy was 131 and 126 mm Hg respectively (not significant) Similarly no significant differences were noted in the PR interval the QRS and the corrected QT interval following short term acebutolol therapy None of the patients had atrioventricular block during therapy One patient developed a single episode of accelerated idioventricular rhythm during sleep However a further increase in the dose of acebutolol in this patient subsequently did not result in a recurrence of this arrhythmia No symptomatic bradyarrhythmias were noted in any of the patients

Side effects during short term therapy (Table I)—Four patients experienced evidence of transient mild gastrointestinal intolerance which did not need dosage adjustment of acebutolol One patient developed a 1 cm increase in heart size on chest x ray with a decreased exercise tolerance after two weeks of acebutolol therapy However the addition of a diuretic agent quickly reversed both the symptoms and the cardiomegaly No hematological or ocular side effects were noted during short term therapy in any patient

Effects of short term acebutolol therapy on angina—All 17 of 20 patients thought to have stable angina by history prior to entering the study had significant subjective decrease in angina following acebutolol therapy However no objective measurements of angina relief by the drug in the form of exercise testing was carried out during the study

Long term trial

The response to long term acebutolol therapy over 12 months in the nine patients is depicted in Fig 2 This figure shows a highly statistically significant and consistent decrease in PVCs from baseline values which was then maintained throughout the 12 month period with only insig

dose of propranolol[14] In the present study the concentration of the acetyl metabolite after oral administration of acebutolol was consistently higher than the plasma concentration of the parent compound Similar results have been reported earlier by Winkle and colleagues[15]

With potential benefits in the management of hypertension[16] and angina,[17] as well as cardiac arrhythmia[3 4] beta blocking agents such as acebutolol enjoy a unique role in treating patients with organic heart disease where the triad of angina hypertension and cardiac arrhythmia often coexist even though the efficacy of acebutolol in each of these three conditions is yet to be well established The results of the present study, along with the other studies on the short term use of acebutolol as an antiarrhythmic agent suggest that this drug may become a useful addition to the clinician s currently inadequate antiarrhythmic armamentarium

Summary

The short term efficacy of oral acebutolol was evaluated in 20 patients with coronary artery disease and frequent premature ventricular contractions (PVCs) by serial 24 hour Holter monitoring before and while the patients were receiving an average daily dose of 1 100 mg of acebutolol for four weeks Fifty five percent of the 20 patients showed a greater than 70% PVC reduction from baseline values The only serious side effect during short term therapy was mild reversible cardiac decompensation in one patient The long term safety and continued efficacy of acebutolol was then evaluated over the next 11 months in nine of the 11 patients showing greater than 70% PVC reduction at four weeks Two thirds of these nine patients continued to show greater than 80 PVC reduction from baseline values at 12 months One patient developed alopecia during long term therapy The majority of patients not responding well to acebutolol at four weeks had an actual increase in PVCs on acebutolol therapy We conclude that acebutolol produces long term effective reduction in PVCs without serious toxicity in the majority of patients with ventricular ectopy However this drug appears to either produce an excellent response or no response with regard to PVC control in most instances

The authors wish to express their appreciation to Ives Laboratories Inc 685 3rd Ave New York for providing the acebutolol and placebo capsules used in this study We also wish to thank Roger L. Williams, M D Medical D[illegible] Drug Studies Unit University of California a S[illegible] for the drug level assays done at his laboratory Dr [illegible] Walls, Ph D., Professor and Head Biometry Division, [illegible]sity of Arkansas Medical Sciences Campus, for the [illegible] analysis of the data Ms. Jean Klemazew[illegible] for [illegible] assistance and Ms Barbara Carter for secretarial [illegible]

REFERENCES

1 Improvement in prognosis of myocardial infarct[illegible] long term beta adrenoreceptor blockade using pract[illegible] A multicentre international study Br Med J 1[illegible] 1975
2 Wilhelmsson C Vedin, J A., Wilhelmsen, L, T[illegible] G., and Werko L. Reduction of sudden death a[illegible] myocardial infarction by treatment with alprenolol [illegible]liminary results, Lancet 2 1157 1974
3 Aronow W S., Turbow M Lurie M Whi[illegible] and Van Camp S Treatment of premature ve[illegible] complexes with acebutolol, Am J Cardiol 41 [illegible] 1979
4 Gradman A. H., Winkle R A Fitzgerald, J W [illegible] P J., Stoner J., III Bell, P A., and Harrison, D C Suppression of premature ventricular con[illegible] acebutolol Circulation 55 785 1977
5 Editorial Side effects of practolol, Br Med J 2[illegible] 1975
6 Meffin P J., Harapat S R., Yee Y G and Harr[illegible] C High pressure liquid chromatographic analys[illegible] drugs in biological fluids V Analysis of aceb[illegible] its major metabolite J Chromatogr 138 18 19[illegible]
7 Morganroth J Michelson E L., Horowitz, L [illegible] Josephson M E. Pearlman A.S and Dunkman, [illegible] Limitations of routine long term electrocard[illegible] monitoring to assess ventricular ectopic frequency C[illegible]culation 58 408 19 8
8 Engler R., Ryan W., LeWinter M Bluestein, H, [illegible] Karliner J S Assessment of lon term an[illegible] therapy studies on the long term efficacy and tol[illegible] tocainide Am J Cardiol 43 61? 1979
9 Danahy D T and Aronow W S Assessment [illegible] rhythmic actions. III Propranolol, Drug Ther [illegible] 2 48 1977
10 Hope R. R., Williams, D O el Sherif N Lazzara [illegible] and Scherlag B J The efficacy of an[illegible] agents during acute myocardial ischaemia and the [illegible] heart rate Circulation 50 507 19 4
11 Gibson D and Sowton E The use of beta adre[illegible] receptor blocking drugs in dysrhythmias, Prog Card[illegible] vasc Dis 12 16 1969
12 Petrie J C., Galloway D B Jeffers T A., and Web[illegible] J Adverse reactions to beta blocking drugs [illegible] Postgrad. Med J 52(Suppl. 4) 63, 19 6.
13 Decalmer P B Chatterjee S S Cruickshank J [illegible] Benson M K., and Sterling, G M Beta blockers [illegible] asthma Br Heart J 40 184 19 8
14 Nies, A. S and Shand D G Clinical pharmacol[illegible] propranolol Circulation 52 6 1975
15 Winkle R A., Meffin, P J., Ricks, W B and Har[illegible] D C Acebutolol metabolite plasma concentration [illegible] Br J Clin Pharmacol 4 [illegible]ing chronic oral therapy 1977
16 Chatterji A N A randomized crossover comparison of [illegible] acebutolol and methyldopa in the treatment of [illegible] moderate essential hypertension Curr Med Res Op[illegible] 5 675 1978
17 Biron P., Tremblay G., and Proulx A. D[illegible] crossover comparison of acebutolol and propranolol [illegible] angina Clin Pharmacol Ther 23 109 19[illegible]

uggests a similar tendency with acebutolol since 5% of the 20 patients showed a greater than 70% VC reduction and 30% had no reduction in VCs from baseline values However a larger atient population will have to be studied before efinite conclusions can be drawn in this regard ince beta blocking agents have been shown to be ost *beneficial in patients displaying evidence* of icreased activity of the autonomic nervous sys em with resting tachycardia[1, 11] it is possible hat patients with ventricular ectopy and slower esting heart rates tend to have a less dramatic esponse to therapy with beta blocking agents ith regard to antiarrhythmic efficacy However n our group of 20 patients even though both of he 11 responders and the nine non respond rs did demonstrate a significant bradycardic esponse from baseline levels the difference in the lecrease in heart rate between the two groups was iot statistically significant Thus an excessive radycardic response or a lack of a bradycardic esponse cannot be said to explain why 55% of our 0 patients showed an excellent response and the emaining 45% showed a poor response or no esponse Since the serum levels of the drug and ts acetyl metabolite were not significantly differ nt in these two groups of patients drug toxicity r inadequate blood levels cannot be said to be he cause of this excellent or poor response with o tendency to obtain intermediate results with cebutolol therapy

Even though the total abolition of complex haracteristics of ventricular ectopy such as pair ng runs of PVC and greater than 10 PVCs per our was not observed with acebutolol therapy in he long term trial it must be considered that the atients in the study population had only sporad c episodes of runs of PVCs both at baseline and during drug therapy and a separate study using patients with more serious and more frequent pisodes of ventricular tachycardia will have to be tudied before a judgment on the efficacy of acebutolol in suppressing complex ventricular arrhythmia can be reached However the present study does suggest that in the small group of patients studied acebutolol is effective in signifi cantly reducing the incidence of isolated PVCs in the majority of patients

Before the safety of acebutolol with long term use can be fully evaluated a much longer experi ence using a much larger patient population than has been observed in the present study will have to be evaluated However in the present study the only patient who needed to have the drug discontinued due to side effects was the single patient who developed alopecia Alopecia has also been noted rarely as a side effect of propranolol therapy The remaining side effects noted were either transient or were reversed by simple coun teractive measures without decreasing the acebu *tolol dosage or stopping the drug Ocular side* effects noted with practolol[5] another beta block ing agent were notably absent with acebutolol in spite of closely monitoring patients for such side effects Likewise no hematological side effects were observed

The present study was not designed to evaluate the relative cardioselectivity of acebutolol Hence in our study the effects of the drug on pulmonary functions could not be commented on since pulmonary functions were not evaluated objectively with spirometry and blood gas deter minations and none of the patients had symp- tomatic chronic obstructive pulmonary disease However the absence of respiratory symptoma tology in our 20 patients during acebutolol thera py is noteworthy Decalmer and colleagues[3] have reported that most of the so called cardioselective beta blocking agents including acebutolol when given to patients with bronchial asthma do pro duce some impairment of ventilatory function But their effects are less depressant in patients with bronchial asthma than the non cardioselec tive beta blocking agents such as propranolol

Even though patients with prior or current cardiac decompensation were excluded from the present study one patient developed mild easily reversible symptoms suggestive of congestive heart failure during the four week trial of acebu tolol Thus as with other beta blocking agents patients with borderline states of cardiac compen *sation who require therapy with drugs such as* acebutolol will have to be observed carefully for evidence of cardiac decompensation

Measurement of serum levels of acebutolol the parent compound and its acetyl metabolite revealed no significant difference in the serum level of either agent between the patients re sponding adequately and the remaining non responders Adequate therapeutic levels for antiarrhythmic efficacy of acebutolol have yet to be worked out fully But the wide range of plasma levels of both agents measured regardless of the therapeutic response and dose is similar to the lack of correlation between plasma propranolol levels in different patients given the same oral

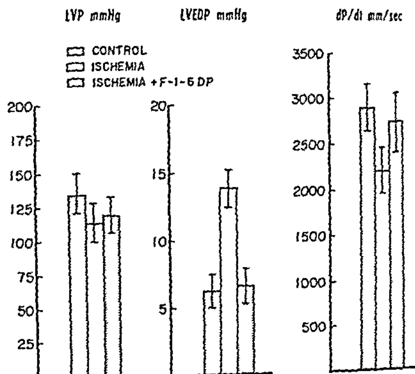


Fig 1 The effect of fructose-1 6-diphosphate (FDP) on left ventricular pressure *(LVP)* left ventricular end-diastolic pressure *(LVEDP)* and the rate of ventricular pressure rise *(dp/dt)* when administered intravenously at 45 minutes after onset of acute myocardial ischemia in 10 dogs The administration of FDP continued as a constant infusion at the rate of 1.25 mg /kg /minute until the termination of the experiment (see text) The standard errors of the mean are indicated.

the femoral vein was used for administration of FDP and other drugs and fluids Prior to induction of ischemia arterial pO_2 pCO_2 pH and CO_2 combining power were verified as to whether they were in physiologic range and if not appropriate adjustments of respiratory volumes and rates were made

Acute myocardial ischemia was induced by either ligating or obstructing a major branch of the left coronary artery with a balloon catheter

Open chest In 10 dogs the heart was suspended in the pericardial sac after thoracotomy and the left anterior descending artery (LAD) was dissected free A control period of 1 hour was allowed prior to ligation of the LAD During this period ventricular and aortic pressures cardiac output measurements and epicardial ECG tracings were recorded The epicardial ECG recordings were unsatisfactory (even though we used cotton wick electrodes suspended on a spring) because artifacts due to motion caused by the respirator made them unreliable Therefore after the ligation of the LAD the chest was closed and precordial ECG was monitored throughout the experiment In this group five animals received FDP and five controls received equimol[ar dex]trose intravenously

Closed chest In 10 closed chest dogs r[...] myocardial ischemia was induced by infla[...] balloon of a Swan Ganz catheter placed [...] fluoroscopic guidance either in the LAD o[...] Such an arrangement permits constant m[...] ing of the coronary perfusion pressure d[...] the occlusion and assessment of the resid[...] in the ischemic muscle segment by pr[...] monitoring of the ^{85}Kr clearance The vo[...] injectate of ^{85}Kr solution was 0.5 ml and [...] flushed with 2 to 2.5 c c of 0.9% NaCl [...] solutions do not have a significant effec[...] given by themselves over periods of [...] seconds during occlusion) In this paired s[...] for the open chest preparations) five [...] received FDP and the others received eq[...] dextrose at the same infusion rate via the [...] nous route

Ischemic period (45 minutes) Once [...] had been induced arterial blood samp[...] taken for gas and pH determinations at [...] utes 30 minutes, and 45 minutes. In some [...] arrhythmias were treated with an intr[...]

·lemodynamic electrocardiographic, and :netabolic effects of fructose diphosphate on cute myocardial ischemia

˜ngel K Markov M D
Nicole C Oglethorpe M S
Thomas M Blake M D
atrick H Lehan M D
Iarper K Hellems M D
Jackson Miss

The myocardial district distal to an arterial obstruction rapidly becomes ischemic and only a limited period of time is available to restore sufficient energy production before the damage becomes irreversible It has long been hoped to fill such a void in anaerobic energy production in the ischemic myocardium by stimulation and acceleration of the Embden Meyerhof pathway This has been done experimentally and clinically administering quantities of glucose insulin and potassium Since Sodi Pollares and associates first reported success with such therapy for acute myocardial infarction many clinical and experimental contradictions have arisen and both the results and the hypotheses used to support early and present claims have in one way or another been challenged[3 8] The most important criterion raised and experimentally documented is that the Embden Meyerhof pathway catabolic activity is not increased but rather impaired by the progressive inactivation of several enzymes in the course of acute myocardial ischemia[1 3] A critical step in ischemic inhibition of glycolysis appears to be inactivation of phosphofructokinase induced by progressively increasing intracellular acidosis[6 1 5] thus depriving the pathway of fructose 1 6-diphosphate (FDP) One approach to relieve this would be to provide FDP exogenously Such an increase in the cytoplasmic concentration of FDP should stimulate glycolysis by intervening as a metabolic regulator and substrate to permit function at higher rates This study was designed to determine experimentally whether such biochemical intervention offers real advantages in protection of acutely ischemic myocardium Two major questions are addressed (1) does intravenous administration of FDP stimulate glycolysis and improve energy production and mechanical function of ischemic myocardium and (2) will this metabolic intervention result in practical benefit and have eventual application in modifying the extent of the ischemic injury in the heart muscle?

Methods

Twenty five mongrel dogs* were used in this study After sedation with morphine sulfate 15 mg (subcutaneous) general anesthesia was induced with pentobarbital 30 mg/kg given intravenously The animals were secured in the left lateral decubitus position intubated and ventilated with a respiratory pump with the use of ambient air Both carotid and jugular veins were dissected free and were used to place catheters under fluoroscopic guidance into the left ventricle pulmonary artery left anterior descending (LAD) or circumflex (CFX) artery and right atrium Another catheter was advanced through a femoral artery to the aortic root while

From the University of Mississippi Medical Center Jackson, Miss.
Received for publication May 23 19 9
Accepted for publication June 15 1979
Reprint requests Angel K. Markov M D Dept. of Medicine University of Mississippi Medical Center 2500 N State St., Jackson Miss. 39216

*The animals used in this study were maintained and used in accordance with the Animal Welfare Act of 1970 and the Guide for the Care and Use of Laboratory Animals prepared by the National Academy of Sciences National Research Council

0002-8703/80/110639 + 08$00 80/0 © 1980 The C V Mosby Co

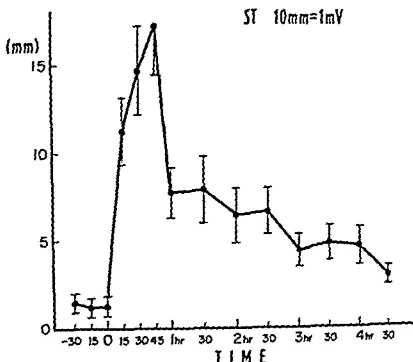


Fig 3 Precordial ST-segment elevation after coronary occlusion and the effect of FDP intravenous administration which began at 45 minutes after the onset of ischemia Values shown are means ± SE (10 dogs)

myocardium were also analyzed for cytochrome oxidase (cyt a_3)[19] and lactate dehydrogenase activity [20]

In five normal anesthetized animals FDP was given intravenously in doses ranging from 100 mg to 2 gm./kg (from 20% stock solution) in order to verify whether this compound has any hemodynamic effects In two animals we studied the ATP and CP in the heart and other organs while in the remainder we studied not only hemodynamic parameters but the plasma half life of FDP and blood lactic acid concentration as well. Also the effect of FDP on the dog erythrocyte metabolism both in vivo and in vitro was assessed This consisted of measuring the ATP and 2 3 DPG content of the erythrocytes and comparing the contents to those that were incubated with glucose

Results

Hemodynamics Occlusion of one of the major branches of the left coronary artery resulted in a drop in mean arterial pressure and left ventricle systolic pressure while the left ventricular end diastolic pressure (LVEDP) began to rise progressively (Figs 1 and 2) The cardiac output also decreased significantly from 4 86 ± 0.56 L/minute to 2 77 ± 0 2 L minute during the ischemic period. Within 7 to 11 minutes after the intravenous administration of FDP the LVEDP began decline from 13.82 ± 3.3 mm Hg and stab[illegible] 6.8 ± 2 0 mm Hg until the termination of [illegible] experiment (Fig 2) The FDP administration caused the left ventricular and aortic pressures rise but they never reached control level (Fig [illegible] The same trend was exhibited by the dp/dt (F[illegible] 1) The negative dp/dt reflected the relaxa[illegible] phase which also improved after the FDP a[illegible] istration The cardiac output after the F[illegible] administration began to increase progress[illegible] and in about 15 to 20 minutes after the admin[illegible] tration of FDP it attained a value of 4.4 ± [illegible] L/minute and remained there until the term[illegible] tion of the experiment The [85]Kr clearance [illegible] the ischemic region in the closed-chest a[illegible] was 11.82 ± 1 6 ml/min/100 gm., while the c[illegible] trol flows were in the range of 104 ± 34 [illegible] min/100 gm By the end of the fourth ho[illegible] [85]Kr clearance increased to 19.36 ± 2.1 ml [illegible] 100 gm. Of the 10 control animals, three [illegible] lated and two had no significant hemodynamic [illegible] ECG changes In the rest the mechanical [illegible] tion of the heart deteriorated progressively

Effect of FDP on ECG In some of the co[illegible] and treated closed-chest animals there was [illegible] elevation of the ST segment prior to occlu[illegible] We attributed this ST segment elevation [illegible]

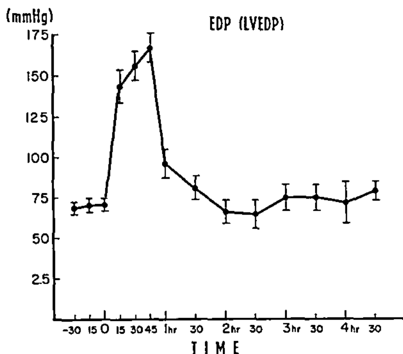


Fig 2 The time response of left ventricular end diastolic pressure *(LVEDP)* to intravenous administration of FDP in 10 dogs with acute myocardial ischemia The FDP administration began at 45 minutes after the onset of ischemia The most pronounced decline of LVEDP was observed during the first 15 minutes after the FDP was given

bolus of lidocaine only during the 45 minute period After FDP or glucose administration had been started (i e at 45 minutes) no drugs were given except for a maintenance dose of anesthetic During this period cardiac output measurements using the thermodilution technique were made at 0 minutes 20 minutes 30 minutes and at 45 minutes and concurrently the other hemodynamic and electrophysiological data were recorded In the closed chest group the coronary blood flow measurements were made 1 minute prior to occlusion and at 30 minutes of ischemia

Ischemia + FDP intervention At 45 minutes of ischemia administration of FDP was started via the femoral vein using a Harvard infusion pump at the rate of 1 25 mg/min/kg A stock solution of 5% FDP prepared 30 minutes prior to administration from fructose 1 6 diphosphate sodium salt (Sigma Chemical Co chemical grade III) was stored in a refrigerator The control animals (10) received 5% dextrose in water at the same rate For the next 4 hours (i e 4 hr and 45 minutes after onset of ischemia) both the treated and control animals received only FDP and glucose at precisely specified concentrations and rates During this period [85]Kr clearance determinations from the ischemic region were made every 30 minutes while hemodynamic and electrophysiological parameters were monitored constantly on a DR 8 Electronics for Medicine recorder Recordings of these data were made every 15 minutes cardiac output determinations were made every 30 minutes At the conclusion of each study (4 hr and 45 minutes) or following ventricular fibrillation the chest was opened and transmural sections from the ischemic and normally perfused myocardium were taken with a specially designed cutting tool that had been cooled in liquid nitrogen These myocardial tissue samples were used for ATP CP lactate and histochemical studies

The frozen transmural sections of both normally perfused and ischemic myocardium were homogenized in 6% perchloric acid and the supernatant was used to determine ATP CP and lactate tissue content The ATP and CP were assayed with the method described by Lamprecht and co workers[16, 17] and the tissue lactate was assayed by the method of Marbach and Weil[8] Sections from ischemic and normally perfused

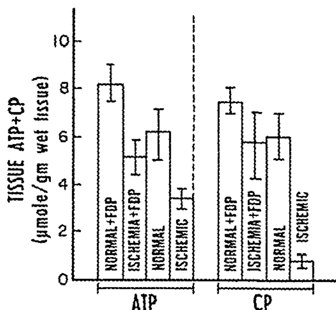


Fig 5 Effects of fructose 1 6 diphosphate *(FDP)* on high energy phosphates in the normally perfused and ischemic myocardium (10 dogs) The effects of FDP on myocardial tissue content of adenosine triphosphate *(ATP)* and creatine phosphate *(CP)* are compared to the control group that received equimolar dextrose (labelled *normal* and *ischemic*) Each column represents the *mean* ± SD

normal and ischemic myocardium (before cytolysis occurs) (2) as a means of indirectly monitoring the oxygen deficit in the ischemic myocardium demonstrated by the low activity of the reduced form of cyt a_3 Histochemically, the activity of cyt a in ischemic tissue was very diminished in both treated and untreated animals (except for the two control dogs that had no hemodynamic nor ECG changes) while LDH activity appeared the same for both groups

The effect of FDP in normal animals In five normal anesthetized dogs the plasma half life was found to be 18 53 ± 1 62 minutes The disappearance rate of FDP when added to dog blood at 37° C was 76% less than when FDP was administered intravenously This indicates that approximately 24% is taken up by the erythrocytes and hydrolyzed prior to being taken up by the different tissues The ATP content of the erythrocytes in the blood incubated for 30 minutes at 37° C was two times higher compared to those that were incubated with equimolar glucose The 2 3 DPG concentration in erythrocytes in vivo and in vitro studies was elevated to the same degree as observed for the ATP Intravenous administration of a total of 500 mg kg over 10 minutes in three anesthetized dogs caused the plasma lactic acid to double within one hour (from 6.21 ± … mg% to 12 8 ± 1 98 mg%) while in most tissues including the heart the ATP and CP content were elevated

Discussion

The glycolytic flux in acute myocardial ischemia in the dog is increased ten to fifteen fold during the transition from aerobic to anaerobic energy production [21, 22] This can supply up to 6% of the energy needs of the ischemic mass Phosphofructokinase activity appears to be rate limiting for glycolysis as shown by the accumulation of glucose 6 phosphate and fructose-6-phosphate [1, 2] Fructose 1 6 diphosphate (FDP) is an intermediate substrate in glycolysis Its depletion in the course of acute ischemia is due to the inactivation of the highly pH sensitive enzyme phosphofructokinase (PFK) which many investigators [14, 15, 23, 24] have attributed to failure of glycolysis to proceed in such conditions The low activity of PFK can be best explained by its properties Kubler and Spieckermann [1] have shown that the activity of PFK is less restricted in experiments with cardioplegia and anoxic perfusion than in ischemic cardiac arrest where lactate production is very slow This implies that PFK is a highly pH dependent enzyme (conclusion similar to that of Mansour [25]) The metabolic acidosis that has taken place inhibits the PFK however when the lactic acid has been washed out from the myocardium and acidosis is corrected Kubler and Spieckermann [1] have observed reactivation of PFK The studies of Mansour on heart phosphofructokinase also confirm that PFK is highly sensitive to acid pH At the very late stage of ischemia glycolysis is again a function of PFK activity simply because there is not enough ATP for phosphorylation of fructose 1 6 diphosphate although there is increased concentration of glucose 6 phosphate and fructose 6 phosphate

As PFK appears to be the limiting step in anaerobic glycolysis the hexokinase and the phosphorylase are of no interest if FDP is the initial step but phosphoglyceraldehyde 3 phosphate dehydrogenase needs a constant supply of NAD to function In ischemic conditions when glucose is the substrate there is conversion accumulation of NADH due to the decreased activity of PFK rather than of pyruvate kinase (PK) It is very important to note that pyruvate

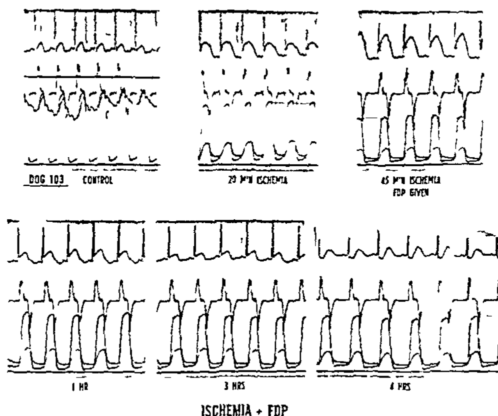


Fig 4 Representative tracing of the electrocardiographic hemodynamic changes in the closed-chest induced acute myocardial ischemia. On the tracing are recorded the precordial ECG left ventricular pressures, dp/dt and peripheral coronary pressure Note the regression of ST segments after the FDP intervention (pressure calibration is 1 mm. = 1 mm. Hg)

he control period to partial coronary artery obstruction by the Swan Ganz catheter (Fig 3) Once the balloon was inflated or the LAD ligated the ST segment began to rise until FDP was given Within 5 to 7 minutes after the administration of the FDP the ST segment began to decline initially very rapidly for about 20 minutes but later it was less pronounced (Figs 3 and 4) Three of the dogs of the control group (10) that received 5% dextrose in water fibrillated (at 1 hr and 14 minutes 1 hr and 32 minutes and at 2 hr and 46 minutes) In five of these animals the precordial ECG demonstrated progressively increasing myocardial injury while in two dogs of the same group only depression of the ST segment was noted after ligation of the LAD After FDP administration began no arrhythmias were observed in any of the treated animals

Effect of FDP on ATP CP and lactate in ischemic and normally perfused myocardium The ATP content in the ischemic muscle segment of the non treated animals showed about 50 to 60% deficit while creatine phosphate (CP) was very low The absolute values of myocardial tissue content of ATP CP and lactate are given in Fig 5 One may notice that in normally perfused myocardium in dogs treated with FDP there was also a noticeable increase in ATP and CP (Fig 5) The tissue lactic acid in the group that received FDP was higher in the normally perfused myocardium than that found in the group that received 5% dextrose in water (Fig 6)

This difference in tissue lactic acid content found in the ischemic muscle in the treated animals was double that found in the ischemic muscle segment of the controls (Fig. 6)

Histochemical results Although these results are not quantitative and do not influence to a great extent the conclusion of this study they were used for the following reasons: (1) in ischemic myocardium the cytoc (cyt a) activity is very low while dehydrogenase (LDH) levels are t

dium These results indicate that FDP intervenes in the Embden Meyerhof pathway not only as a high energy substrate but also as a metabolic regulator influencing the activity of phosphofructokinase and that of pyruvate kinase FDP also stimulates glycolysis in dog erythrocytes and increases their ATP and 2 3 DPG content by a factor of 2

The most significant finding in these studies is that this biochemical intervention appears to restore the depressed activity of glycolysis in ischemic myocardium

REFERENCES

1 Sodi Pallares D Possibility of a therapy of cellular ion integration in cardiovascular diseases Arch Inst Cardiol Mex **31** 557 1961
2 Sodi Pallares D Ponce de Leon J Bisteni A and Medrano G A Potassium glucose and insulin in myocardial infarction Lancet **1** 1315 1969
3 Danforth W H, Naegle S, and Bing R J Effect of ischemia and reoxygenation on glycolytic reactions and adenosine triphosphate in heart muscle Circ Res **8** 965 1960
4 Cornblath M Randle P J Parmeggiani A and Morgan H D Regulation of production glycogen content and phosphorylase activity in the isolated perfused rat heart J Biol Chem **238** 1592 1963
5 Opie L H Metabolism of the heart in health and disease Part I AM HEART J **76** 685 1968
6 Fletcher G F Hurst J W and Schlant R C Polarizing" solutions in patients with acute myocardial infarction a double blind study with negative results AM HEART J **75** 319 1968
7 Pentecost B L Mayne N M and Lamb P Controlled trial of intravenous glucose potassium and insulin in acute myocardial infarction Lancet **1** 946 1968
8 Report of the Medical Research Council Working Party on the Treatment of Myocardial Infarction Potassium glucose and insulin treatment for acute myocardial infarction Lancet **2** 1355 1968
9 Lesch M Teichholz L E Soeldner J S and Gorlin R Ineffectiveness of glucose potassium and insulin infusion during stress in chronic heart disease Circulation **49** 1028 1977
10 Williamson J R Glycolytic control mechanisms II Kinetics of intermediate changes during the aerobic anoxic transition in perfused rat heart J Biol Chem **241** 5026 1966
11 Rovetto M J Lamberton W F and Neely J R Mechanisms of glycolytic inhibition in ischemic rat hearts Circ Res **37** 742 1976
12 Liedtke A J Hughes H C and Neely J R Effect of excess glucose and insulin on glycolytic metabolism during experimental myocardial ischemia Am J Cardiol **38** 17 1976
13 Rovetto M J Whitmer J T and Neely J R Comparison of the effects of anoxia and whole heart ischemia on carbohydrate utilization in isolated working rat hearts Circ Res **32** 699 1973
14 Williamson J R Metabolic control in the perfused heart *in* Control in Energy Metabolism, B Chance R W Estabrook, and J R Williamson, eds, New York 1965 Academic Press Inc pp 333 346
15 Mansour T E Studies on heart phosphofructokinase purification inhibition and activation J Biol Chem **238** 2285 1963
16 Lamprecht W and Stein P *Methods of Enzymatic Analysis* H V Bergmeyer ed New York, 1963 Academic Press Inc p 610
17 Lamprecht W and Trautschold I *In* Methods of Enzymatic Analysis H V Bergmeyer ed, New York 1963 Academic Press p 546
18 Marbach E P and Weil M H *Rapid enzymatic measurement of blood lactate and pyruvate*, Clin Chem **13** 314 1967
19 Burstone M S *Modification of histochemical techniques for the demonstration of cytochrome oxidase* J Histochem Cytochem *9* 59 1961
20 Pearse A G E Histochemistry Theoretical and Applied Boston 1968 Little Brown & Company p 1344
21 Kubler W, and Spieckermann P G *Regulation of glycolysis in the ischemic and anoxic myocardium* J Moll Cell Cardiol **1** 351 1970
22 Opie L H and Owen P Glycolysis in acute experimental myocardial infarction Pathways of metabolism preliminary results *in* Recent Advances in Studies on Cardiac Structure and Metabolism Baltimore, 19 University Park Press Vol 2 pp 567-578
23 Wollenberger A and Krause E G Activation of a glucan phosphorylase and related metabolic changes dog myocardium following arrest of blood flow Biochem Biophys Acta **67** 337 1963
24 Wollenberger A and Krause E G Metabolic control characteristics of the acutely ischemic myocardium, Am J Cardiol **22** 349 1968
25 Taylor G B and Bailey E Activation of liver pyruvate kinase by fructose 1 6 diphosphate Biochem J 102 1967
26 Iurovitskii I U G and Milman L S Regulation of pyruvate kinase activity by fructose 1 6-diphosphate the developing embryo Doklady Akademii Nauk **175** 1404 1967
27 Hess B et al FDP activation of yeast pyruvate kinase Biochem Biophys Res Comm **24** 824 1966
28 Solomos P Observations on yeast pyruvate kinase activity in vivo Biochem Biophys Res Comm 40 1970
29 Principles of Biochemistry fifth edition Eds A P Handler and E Smith New York 1973 McGraw Book Company pp 436-477
30 Passonneau, J V and Lowry D M P fructokinase the control of the citric acid cycle Biochem Biophys Res Comm **13** 372 1963
31 Soscia F, Nuniata A Costrini R, et al FDP on blood ATP and glucose (In press)
32 Valletta J and Sagaut P L'Esafosfina, un alimentation parenterale post-operatoire Cah Anest **23** 2 75 1955
33 Avogaro P et al FDP nel trattamento di pazienti nemici (In press)

kinase needs FDP as an allosteric cofactor which directly stimulates its activity This influence of FDP on pyruvate kinase activity has been observed in the liver[25] developing embryo and in yeast[27, 28] When PFK is activated there is no available FDP which is needed for the PK to operate at optimal reaction velocity for the production of pyruvate hence no substrate for lactate dehydrogenase to generate NAD There fore it appears that the presence of FDP is necessary not only as a substrate but as a metabolic regulator in order for the glycolysis to function at the level of the trioses

Another important catalytic activity of FDP is its direct feedback action on phosphofructokinase (PFK) The activity of PFK is stimulated by ADP AMP and inhibited by ATP citrate[3] and acidosis FDP in high concentration removes this inhibition of ATP citrate and acidosis This has been shown in this study and indirectly supported by the fact that the FDP administra tion in man induces lactic acid increase and increased glucose utilization[31, 3] Theoretically such an increase in ATP/ADP ratio induced by the FDP disinhibition of PFK could be main tained as long as an excess of FDP exists in cytosol in both normally perfused or ischemic tissue (provided that there is still some residual flow) The other advantage of using FDP as a substrate in acute ischemia and any energy defi cient states is obvious the rate limiting enzymes above PFK are eliminated and those below are no longer inhibited From an energetic point of view the advantage of using FDP as the initial sub strate for glycolysis is that the net yield of the anaerobic metabolism of one mole of glucose is 2 ATP while if one mole of FDP is metabolized in the same conditions it will produce 4 ATP because there is no phosphorylation of glucose and fructose 6 phosphate reactions which re quire utilization of ATP On the other hand while doubling the quantity of ATP produced lactate production remains the same as though one mole of glucose had been metabolized It is obvious that in order to obtain the same results in the direction of making usable energy available from FDP it is necessary to administer it in large quantities (on the order of several grams) (The LD_{50} of FDP when administered at the rate of 500 mg /minute in dogs is approximately 5 8 to 6 gm /kg)

Another important finding in this study is that

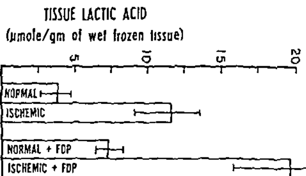


Fig 6 The mean myocardial tissue lactate content in the normally perfused ischemic myocardium for the group that received 5% dextrose in water (the two columns on the *left*) and the group that was treated with fructose 1 6-diphosphate *(FDP)* on the *right* Note that the value for ischemic myocar dium from the dogs that received FDP is almost double that found in the controls

FDP causes a substantial increase of 2 3 DPG in the erythrocytes This increase of 2 3 DPG is of importance for the oxygen exchange between hemoglobin and tissue It also contributes per haps in a lesser manner by increasing the oxygen available to the marginal heart muscle surround ing the ischemic tissue

The results of this study demonstrate that FDP when given to dogs with experimentally induced acute regional myocardial ischemia improves the mechanical function of the heart causes regression of electrocardiographic ischemic changes and increases significantly the ATP and creatine phosphate in both ischemic and normal ly perfused myocardium Extrapolating from these results it appears that FDP can indeed restore the depressed activity of the Embden Meyerhof pathway in ischemic myocardium

These conclusions suggest a rational basis for employing FDP in clinical situations as an agent to limit or decrease infarct size in acute myocar dial infarction

Summary

The hemodynamic electrocardiographic and metabolic responses of dogs with acute myocar dial ischemia to intravenous administration of fructose 1 6-diphosphate (FDP) were assessed

Analysis of the results (compared to dextrose control) revealed evidence of major improvement of LVEDP and cardiac output significant decrease of the ST segment and large increases of ATP and CP in the ischemic district and to a lesser degree in the normally perfused myocar

Table I Study groups with myocardial ischemia

	Non treated control	*Aspirin treated*	*Indomethacin treated*
Number of animals	36	20	20
Hemodynamics	8	10	9
ECG mapping	18	10	9
Platelet Cr and In studies	11	4	—
Tissue electrolytes	9	8	9
Plasma FFA	8	7	9

before the induction of ischemia the balloon was inflated with 1 ml of air and peripheral coronary pressure was monitored using a Statham strain gauge Complete coronary occlusion was evidenced by a reduction of mean peripheral coronary pressure to approximately 30 mm Hg and by the appearance of an injury potential on standard Lead I No antiarrhythmic drugs were used and animals that fibrillated within the initial 15 minute high risk period were excluded from the study Thus four animals of the non treated group three of the indomethacin treated group and one of the aspirin treated group were excluded from the study These eight animals were not included in the group of 76 animals shown in Table I The experiment was designed for a four hour ischemic period during which hemodynamic parameters and electrocardiograms were continuously monitored and were intermittently recorded along with cardiac output Estimated size of the ischemic area was made during the four hour period from 20 precordial ECG leads determining the number with ST elevation (N ST) and the sum of the ST elevation (ΣST) using an electrical calibration of 0 1 mV[9] Serial arterial blood samples were taken from both groups for the plasma free fatty acid determination method As described before [1, 11] microcirculatory thrombosis was determined at the end of the four hour balloon occlusion by taking multiple myocardial tissue samples from the region of the obstructed coronary artery and the contralateral non ischemic area from animals preinfused with [5]Cr or [11]In Microcirculatory thrombosis was expressed as the radioactivity ratio of the multiple tissue samples taken from the ischemic and non ischemic areas

At the conclusion of the studies the thorax was incised and the heart was rapidly arrested with iced Ringer s solution The ischemic area of the left ventricle was excised parallel to a d l ... lateral to the anterior descending artery beginning 1 cm below the obstruction site down to the apex and then perpendicular to the a... descending artery across to the terminatio of ... most inferior diagonal branch or an ... extension when this branch terminates short of the apical level The outer margin was formed ... the termination of the main epicardial segment of the other diagonal branches This formed a approximately triangularly shaped sample with the base at the cardiac apex and the peak ... below the obstruction site In previous studies ... have observed that injection of Evans Bl e d... distal to the obstruction site at diastolic press... levels stains this area except where there ... aberrant vessel distribution [12] Such animal ... excluded from this study A similar size segme... approximating 12 g was taken from the no... ischemic posterior wall In view of the poten... heterogeneity of the myocardial metabo... response the ventricle was divided into inner a... outer layers the tip of the papillary muscle ... excluded and the epicardial adipose tissue ... removed To analyze for sodium and pota... concentrations samples were homogenized a... extracted for 48 to 72 hours in distilled wate... sufficient time for complete extraction Po... sium and sodium were determined in duplicate ... an Auto Analyzer system with flame attachme... Water content was determined by drying samp... in an oven at 100 °C to constant weight

In evaluation of the results the study was ... with regard to precordial ECG mapping ... analysis for electrolytes and water and pla... free fatty acid levels For statistical analy... Student s t test for paired and non paired obse... vations was used when appropriate Mortal... rates were assessed by the χ^2 formula

Results

Table I summarizes the groups studied as ... as the number of animals and the procedures ... to assess the effects of aspirin and indometha... in the animals subjected to a four hour ... thrombotic coronary occlusion For the ... tion of results the number of animals used f... each group was felt to be adequate for provid... statistically analyzable information with co... parable numbers of animals among the gro... and for each category of parameters Com... and for each category of parameters ... hemodynamic changes during the four hour ...

Chronic use of aspirin versus indomethacin during non-thrombotic myocardial ischemia effects on survival

Christos B Moschos M D
Bunyad Haider M D
Amparo J Escobinas B S
Ashwinkumar Gandhi M S
Timothy J Regan M D
Newark N J

Our previous studies on the effects of chronic treatment of aspirin (ASA) upon acute non thrombotic coronary occlusion in dogs showed that this analgesic was effective in significantly decreasing the incidence of ventricular fibrillation associated with a reduction of sodium and water accumulation and potassium loss in ischemic tissue[1] On the other hand recent reports on indomethacin an analgesic with action upon platelet function and prostaglandin metabolism described as similar to that of ASA[2,3] showed that when given acutely ischemia induced by coronary ligation was enhanced [3] In view of this disparity as well as other differences related to the regulation of myocardial blood flow[5] we have utilized a closed chest canine model to study the effects of chronic treatment with indomethacin upon arrhythmias during non thrombotic coronary occlusion and compare its effectiveness with that of ASA

Methods

A total of 76 apparently healthy male mongrel dogs weighing 20 to 26 kilograms were used and were divided into two groups Group A (N = 20) treated with aspirin 600 mg daily and Group B (N = 20) treated with indomethacin 25 mg /day The doses of the two drugs are moderate therapeutic schedules calculated on the basis of body weight Both groups were treated for seven consecutive days prior to the day of the experiments A group of 36 dogs served as non treated controls After an 18 hour fast all animals on the day of the experiment were anesthetized with morphine sulfate (3 mg /kg intramuscularly) and sodium pentobarbital (20 mg /kg intravenously) and were subsequently placed on a respiratory pump to maintain adequate ventilation Frequent pH determinations were performed to confirm maintenance within the physiologic range The left jugular vein and left and right carotid arteries were exposed through small skin incisions Number 8F catheters were passed into the left ventricle via the right carotid artery and the root of the aorta via the femoral artery Left ventricular and aortic pressures were recorded by means of Statham strain gauge transducers using an Electronics for Medicine DR 8 amplifier recorder Cardiac output was determined by the thermodilution technique with the thermodilution catheter placed in the main pulmonary artery via the jugular vein[6] All animals were under continuous electrocardiographic monitoring

Myocardial ischemia was induced by means of a double lumen balloon tipped catheter inserted through the left carotid artery and positioned under fluoroscopic control in the left anterior descending coronary artery approximately 2 5 cm from its origin as described before[1] After determining control hemodynamic parameters

From the College of Medicine and Dentistry of New Jersey—New Jersey Medical School, Department of Medicine Newark.

Supported by United States Public Health Service Research Grant Number HL 13036.

Received for publication June 8 1979

Accepted for publication Oct. 9 1979

Reprint requests Christos B Moschos, M D CMDNJ New Jersey Medical School 100 Bergen St. MSB I-5 8 Newark N J 07103.

000?-8 03/80/110647 + 06$00 60/0 © 1980 The C V Mosby Co

Table IV Left ventricular electrolytes after four hours of ischemia

	H_2O%						Na (μEq/g)						K (μEq/g)					
	Untreated (9)		ASA (8)		Indo (9)		Untreated (9)		ASA (8)		Indo (9)		Untreated (9)		ASA (9)		Indo [illegible]	
	N	I	N	I	N	I	N	I	N	I	N	I	N	I	N	I	N	I
Inner layer	80 6 ±0 5	84 4 ±0 6	77 3 ±0 9	80 4 ±1 0	79 4 ±0 4	82.2 ±0 5	36 7 ±1.2	64 0 ±8 7	38 0 ±2 0	57 0 ±4 1	45 7 ±2 1	67 4 ±4 3	71 9 ±2 0	33 0 ±2 5	6[illegible] 0 ±2.2	48 0 ±3 [illegible]	73 33	[illegible]
Mid layer	81 0 ±0 5	83 5 ±0 4	78 1 ±0 6	79 7 ±1 0	79 4 ±0 5	82 3 ±0 9	36.3 ±1 0	67 0 ±7 4	36 0 ±1 6	52 0 ±3 2	42 1 ±2.6	60 7 ±3 6	69 6 ±0 9	38 0 ±3 9	69 6 ±0 6	54 0 ±3 5	71 43	[illegible]
Outer layer	80 4 ±0 5	83 7 ±0 8	77 7 ±0 8	79 1 ±0 9	78 3 ±0 4	79 8 ±1 1	33 2 ±1 0	72 0 ±7 8	37 0 ±2 0	50 0† ±4 6	44 2 ±1 9	54 4 ±3.2	72 7 ±1 6	46 0 ±6 3	78 0 ±5 6	56 0 ±3 4	60 36	[illegible]

P = 0 01
†P = 0 05

when compared to both the non treated group and the indomethacin treated group ($P < 0.02$) Table VII shows radioactivity from labelled platelets in tissue samples from the ischemic and non ischemic areas indicating that only when thrombus was obstructing the left anterior descending coronary artery was there significant accumulation of platelets in the microcirculation, suggested by the significant ratio of ischemic to non ischemic tissue With balloon obstruction there were no differences when compared to non treated or to aspirin treated animals

Discussion

The results of the study suggest that in the absence of a thrombotic process in the coronary arteries aspirin pretreatment appears to be capable of modifying survival associated with balloon obstruction of the coronary artery In contrast, pretreatment with indomethacin failed to reduce mortality rate which was the same as the one observed in the non treated animals Analysis of the data obtained in the study indicates that whereas the hemodynamic changes were not consistent among the three groups myocardial injury following balloon occlusion appeared to be of lower magnitude in the aspirin group at the end of the four hour period when compared to its own control Since water and cation changes after four hours of ischemia were less extensive in the aspirin group one could postulate on the contribution of more extensive tissue swelling in the non treated as well as in the indomethacin treated group contributing to local changes generating more intensive ischemia and higher incidence of fatal arrhythmias

It should be noted that loss of potassium in the indomethacin group was the smallest among the three groups Since in studies by others [illegible] shown that in the animals receiving indomethacin regional and collateral blood flow [illegible] decreased the observed decrease in pota[illegible] loss in the indomethacin group could be a [illegible] related phenomenon A lower perfusion [illegible] could result in a greater accumulation of K [illegible] leaked from the cardiac cell in the interstit[illegible]

This study raises the question regarding the mode of action of the antiplatelet agents, at the cyclo oxygenase level, namely whether the action is indeed non selective affecting indiscr[illegible] inately the enzyme responsible for the genera[illegible] of the opposing prostaglandins stored in pla[illegible] and the vascular endothelium Recent [illegible] suggest that aspirin in small amounts block[illegible] preferentially platelet cyclo oxygenase and the[illegible] fore the generation of thromboxane-A [illegible] allowing its counterpart prostacyclin stored [illegible] the vascular endothelium to exert its vasod[illegible] ing and platelet antiaggregating effect.[illegible] action was also implied by the studies of Cap[illegible] and colleagues[14] who found that aspirin pre[illegible] ment increased collateral flow after co[illegible] occlusion in dogs[14] In the studies of Korb[illegible] Moncada[13] it was found that aspirin in do[illegible] 150 mg/kg blocked both platelet and endoth[illegible] prostaglandin However using 10 mg/kg th[illegible] investigators described a net effect in fa[illegible] prostacyclin [illegible] The results obtained in our [illegible] could be relevant to the observation made [illegible] Korbut and Moncada with their lower a[illegible] dose since the dose of 30 mg/kg, although [illegible] than 10 mg/kg is still within the usual th[illegible]

Table II Hemodynamic parameters

	Control			*60 minutes*			*4 hours*		
	Untreated (8)	*ASA (10)*	*Indo (9)*	*Untreated*	*ASA*	*Indo*	*Untreated*	*ASA*	*Indo*
Heart rate (beats/min)	147±9 0	131±7 9	155±1?.9	14?± 8 1	1?6±6 7	149±6 1	135±9 3	120± 8 6	147±6 8
Aortic pressure (mm Hg)	139±8.2	119±7.2	159± 2 4	1?7±10 1	1?0±8 4	148±2 4	133±3 6	117±10 3	147±2.9†
LVEDP pressure (mm Hg)	12±2 0	10±1.2	13± 0 9	12± 1 2	11±1 2	16±1 3†	16±3 1	14± 1 3†	?0±2.2
SV (mL)	27 1± 5	17 8±2 5	24.5±2 2	24 4± 1 2	16 2±1 [illegible]	25 1±3 0	16 0±1 9	14 8± 1 6	20 0±1 8

P = 0 01
†P = 0 05

Table III Electrocardiographic mapping

Time post-occlusion	*15 min*	*1 hour*	*4 hours*
NST			
Non treated	14 00 ± 1 11	12 7? ± 1 23	13.53 ± 1.25
Aspirin treated	1? 40 ± 1.52	11 7 ± 1 06	9 38 ± 1 34
Indomethacin treated	9 0 ± 0 53	8 0 ± 1 6?	9 0 ± 1 09
ΣST (mV)			
Non treated	4 41 ± 0 ?4	4.21 ± 0 52	4 53 ± 0 ?3
Aspirin treated	6 25 ± 1 60	6 09 ± 1 33	4 23 ± 0 89
Indomethacin treated	3 56 ± 0 ?3	3 41 ± 1 09	3 69 ± 1 02

nary occlusion in the treated and non treated animals (Table II) aortic pressure in the indomethacin treated group appears to be at levels suggestive of hypertension a described side effect of indomethacin Subsequently over the four hour period systemic pressure fell with a concomitant rise in the left ventricular end diastolic pressure to levels that were significant when compared to control In contrast pressure changes in the non treated and aspirin treated groups were less consistent showing a significant end diastolic pressure rise in the aspirin group and a significant decrease in stroke volume in the non treated group There were no significant changes in heart rate among treated and non treated groups Precordial ECG mapping (Table III) showed that the degree of ischemia over the four hour period of observation remained practically unchanged from the non treated and the indomethacin treated animals whereas in the aspirin group there was a gradual decrease in the extent of ischemia although the observed differences were not statistically significant

Table IV shows changes in water content and electrolyte concentrations in the ischemic cardiac tissue In the aspirin treated group water accumulation was significantly less in all layers when compared to the non treated group In the indomethacin group the increased tissue water was somewhat less than in the non treated group but more than in the aspirin treated group in the inner and middle layers Sodium increments were of smaller magnitude in the aspirin treated group statistically significantly different from the non treated animals in the outer and mid layers In the indomethacin group the gain of sodium was consistently more in all three layers However while potassium loss from ischemic tissue was reduced in the aspirin group particularly in the endocardial layers it was even more so in the indomethacin group when compared to the non treated group Free fatty acid determination in all groups showed that the expected rise in FFA in ischemia was aborted in the aspirin as well as the indomethacin treated animals (Table V)

Comparing mortality rates in the three groups (Table VI) it was found that in the aspirin treated group mortality rate was significantly less

sodium and water abnormalities of the ischemic tissue These changes were not related to consistent abnormalities in hemodynamic parameters or evidence of microcirculatory thrombosis

Summary

In view of the reported disparity of the effects upon ischemic myocardium of aspirin and indomethacin both affecting platelet function and prostaglandin metabolism we utilized a closed chest canine model to study the effects of chronic treatment with these agents upon arrhythmias during non thrombotic coronary occlusion Group A (N = 20) and Group B (N = 20) were pretreated for seven consecutive days with aspirin 600 mg /day and with indomethacin 25 mg /day respectively A group of 36 non treated animals served as controls Determination of hemodynamics revealed no significant differences in left ventricular function among the various groups although blood pressure levels were consistently higher in Group B Precordial ECG mapping showed lower magnitude of myocardial ischemia in the aspirin group Changes in water and cation composition of the ischemic tissue after four hours of coronary occlusion were also significantly lower in the aspirin group suggesting that more extensive tissue swelling in the indomethacin group might have contributed by means of more intensive ischemia to a higher incidence of ventricular fibrillation Consistently higher blood pressure levels requiring increased mechanical demands on the myocardium would enhance the negative results observed in the indomethacin group Mortality rate was 5% for the aspirin group versus 40% and 39% for the indomethacin and the non treated groups respectively ($P < 0.015$) The failure to observe significant platelet accumulation by radioactivity counts in either treated or non treated animals using [51]Cr and [111]In labelled platelet indicated that microcirculatory thrombosis was not a feature in this model It is not clear to what extent the reported diverse mostly inhibitory effects upon the various enzyme systems and lysosomal membrane ascribed to anti inflammatory agents are applicable more for indomethacin per se or for the therapeutic schedule used in this study in order to explain its different effect upon ischemic myocardium

REFERENCES

1 Moschos C B [illegible] B DeLa Cruz C Lyons M M and Regan T J Antiarrhythmic effects of aspirin during non thrombotic coronary occlusion, Circ 57 681 1978
2 Wolfson S Tacket C Good N hirmser R J [illegible] bo M and Cohen L S Role of prostaglandin [illegible] coronary occlusion Circulation 56 III [illegible]
3 Jugdutt B I Hutchins G M Bulkley B H [illegible] and Becker L C Effect of indomethacin on coronary blood flow and infarct collateral blood flow after coronary artery occlusion in the conscious dogs, Circulation 59 794 1979
4 Berger H J Zaret B L Speroff L Cohen L S and Wolfson S Regional cardiac prostaglandin release during myocardial ischemia in anesthetized dogs, Circ [illegible] 38 566 1976
5 Kraemer R J Phernetton T M and Folts J E Prostaglandin like substances in coronary venous [illegible] flow following myocardial ischemia J Pharmacol Exp Ther 199 611 1976
6 Owen L T Ehkart I C Weidner J W Scott J B and Haddy F J Effect of indomethacin on local [illegible] flow regulation in canine heart and kidney [illegible] Biol Med 149 871 19 5
7 Hintze T H and Kaley G Prostaglandins and the controls of blood flow in the canine myocardium, Circ Res. 40 313 1977
8 Ganz W Donoso R Marcus H Forrester J [illegible] Swan H J A new technique for measurement of cardiac output by thermodilution in man Am J Cardiol 27 [illegible] 1971
9 Maroko P Kjekshus J Sobel B Watanabe T C[illegible] ell J Ross J Jr and Braunwald E Factors influencing infarct size following experimental coronary occlusion Circulation 43 67 1971
10 Kelley T F Improved method of microtitration of [illegible] acids Anal Chem 37 1078 1965
11 Moschos C B Lahiri K Lyons M M Weese J [illegible] Oldewurtel H A and Regan T J Relation of microcirculatory thrombosis to thrombus in the proximal coronary artery Effects of aspirin dipyridamole and thrombolysis AM HEART J 86 61 1973
12 Regan T J Harman M A Lehan P H Burke W [illegible] and Oldewurtel H A Ventricular arrhythmias and [illegible] transfer during myocardial ischemia and intervention with procaineamide insulin or glucose solution J Clin Invest 46 1657 1967
13 Korbut R and Moncada S Prostacyclin (PGI) and thromboxane A interaction in vivo Regulation by aspirin and relationship with antithrombotic therapy Thromb Res 13 489 1978
14 Capurro N L Marr K C Aamodt R Goldstein R E and Epstein S E Aspirin induced increase in collateral flow after acute coronary occlusion in dogs, Circulation 59 744 19 9
15 Crook D and Collins A J Comparison of effects of aspirin and indomethacin on human platelet prostaglandin synthetase Ann Rheum Dis 36 4 9 19[illegible]
16 Flower R J Drugs which inhibit prostaglandin biosynthesis Pharmacol Rev 26 33 1974
17 Whitehouse M W and Haslam J M Ability of some anti rheumatic drugs to uncouple oxidative phosphorylation Nature 196 1323 1962
18 Shen T Y Perspectives in nonsteroidal anti-inflammatory agents Angew Chem Int. Edit. 11 460 19[illegible]
19 Rennick R B Renal tubular transport of prostaglandins Inhibition of probenecid and indomethacin Am J Physiol. 233 F 133 19 7
20 Ogletree M L and Lefer A M Prostaglandin [illegible] preservation of the ischemic myocardium Circ Res 42 218 19 8

Table V Free fatty acid in treated and untreated groups (μEq/L)

	No	Before myocardial ischemia	After 4 hours coronary occlusion	P
Non treated	8	210±38	696±246	<0 05
Aspirin	7	232±46	287±42	NS
Indomethacin	9	*437±60*	*519±80*	*NS*

NS = not significant

peutic levels and much closer to them than the dose of 150 mg /kg These observations are consistent with previous studies describing differences in the effect of aspirin and indomethacin upon platelet prostaglandin synthetase It was found that aspirin induced a long lasting or irreversible inhibition of platelet prostaglandin synthetase whereas *indomethacin inhibited the enzyme for* only a short period of time which might have expectedly cancelled a favorable effect of a non antagonized endothelial prostacyclin such as described for aspirin [13 15] These findings then could explain at least in part the beneficial effect observed in the aspirin treated group and the negative results observed in our indomethacin treated animals which were consistent with observations indicating the adverse effect of this prostaglandin inhibitor upon ischemic myocardium [5] Since the *absolute level of blood pressure* in the indomethacin treated animals was higher than that of the other groups the adverse effect of this parameter requiring increased mechanical demands on the myocardium will have to be also considered in explaining the negative results observed in the indomethacin group Moreover it has been pointed out that prostaglandin inhibitors exert with plasma levels achieved with therapeutic doses such as used in our study inhibitory effect upon a variety of other enzymes and cellular systems Among anti inflammatory agents indomethacin used as a reference compound was documented as affecting a host of enzymes [8] and in addition to inhibiting prostaglandin synthetase was also described as blocking membrane transport of prostaglandins and therefore access to their *environment* and *interference with pro*tection of ischemic myocardium Whether such inhibitory activity is more consistent among the other inhibitors for indomethacin per se at the doses given in our studies is not clear However

Table VI Mortality in treated and untreated groups

	N	Mortality	P*
Non treated	36	14 (39%)	
INDO-treated	20	8 (40%)	NS
ASA treated	20	1 (5)	0 015

P INDO vs ASA = 0 02.

Table VII Radioactive platelet distribution after four hour coronary occlusion

	N	Radioisotope	Mode Of occlusion	LAD/C ratio
Control	4	Cr	None	1 0
	2	In	None	1 0
Ischemic	8	Cr	Thrombus	3 30
untreated	7	Cr	Balloon	1.30†
	4	In	Balloon	0 93†
Ischemic aspirin treated	4	Cr	Balloon	1 44†

P < 0 01
†P = NS.

its reported diverse effects upon the various enzyme systems and lysosomal membrane could render the observed unfavorable effects of indomethacin upon ischemic myocardium plausible It is worth noting that in most of the experimental studies with indomethacin the compound was administered to open chested or preinstrumented animals and the doses used were far in excess of suggested therapeutic levels per weight unit In contrast the results in our studies were obtained by long term daily administration of indomethacin at conventional therapeutic doses in animals that remained intact throughout the treatment and experimental period

The failure to observe significant platelet accumulation by radioactivity counts in either treated or non treated animals using ^{51}Cr or ^{111}In indicated that microcirculatory thrombosis is not the issue in this model.

The aborted free fatty acid rise in both treated groups might also be discounted in explaining mortality rate differences among the treated groups Presently the exact mode of action of the *anti inflammatory agents in this model* and this species eludes a clear understanding It appears then that pretreatment with relatively low dose of aspirin was accompanied by lower incidence of ventricular fibrillation and by lower degree of

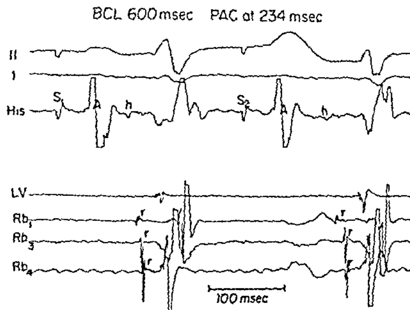


Fig 1 This figure shows the last of nine depolarizations that resulted from right atrial drive at 600 msec basic cycle length and also the depolarization produced by premature right atrial drive at 234 msec. Electrograms (from top to bottom) II and I represent electrocardiograms from ECG Leads II and I His represents the recordin from a His bundle catheter inserted into the aortic root Deflection S_1 is the stimulus artifact A is the atrial depolarization h is the His bundle activation which is followed in turn by the activation of the high septal myocardium and S_2 is the second and premature stimulus artifact. LV electrogram is recorded from bipolar electrodes in the left ventricular apex and shows some Purkinje activation and activation time of the left ve [illegible] Rb, electrogram shows the activation of the proximal right bundle (r) followed by activation of the underlying right ventricular septum Rb_3 represents an electrogram 6 mm more distal on the right bundle showing right bundle activation (r) and mid right septal activation Pb_4 represents the right bundle activation 9 mm more distal from the Rb electrode The second complex is premature and shows conduction delay above the His bundle (increased A H interval) and conduction delay in the proximal right bundle branch of 15 msec.

the proximal right bundle as it emerged onto the surface of the right ventricular septum A typical example of the activation sequence of a normal and premature beat is shown in Fig 1 The first complex shown represents the response to the last of nine regular stimuli given at 600 msec cycle lengths Note that the His bundle activation is quickly followed by activation of the proximal right bundle branch (electrode Rb) and then at electrodes 6 and 9 mm more distal (Rb_3 and Rb) The muscle activation can be seen to occur earliest in the more distal right bundle electrodes and later near the proximal right bundle electrodes located in the upper right ventricular septum The time of activation of both the right and left ventricular endocardium is nearly simultaneous The second complex of Fig 1 is the least premature impulse that would not produce FRBBB Note the similar activation of the second complex sequence to the first complex and compare the delay of conduction that occurs in the proximal right bundle branch between e[illegible] trodes Rb, and Rb, The degree of con[illegible] delay shown here is the maximum attai[illegible] nine experiments before blockage of cond[illegible] would occur

Fig 2 shows the effect of making the prem[illegible] stimuli more premature by only 4 msec [illegible] same animal The activation sequence [illegible] quite different in the second complex [illegible] the FRBBB There is no apparent activat[illegible] the right bundle distal to the most prox[illegible] electrode The activation of the right ventr[illegible] myocardium now lags behind that of the [illegible] ventricle consistent with the delay of activ[illegible] of the right ventricle In these experiments, [illegible] visualization of the activation front as rec[illegible] by the electrodes was never noted witho[illegible] seeing delay in activation of the right ventr[illegible] myocardium In every instance of FRBBB [illegible] duced in each of the nine experiments, the [illegible] loss of recording of right bundle activ[illegible]

Site of functional right bundle branch block

Chalmers Lyons M D F.A C C
Salt Lake City Utah and Albany N Y

There has been considerable speculation as to the site and mechanism of functional right bundle branch block (FRBBB) Certain investigators believe that the site of conduction block is at the distal end of the right bundle while other workers favor a more proximal site[5 11] The present work was undertaken to document the site of functional right bundle branch by placing a 36 electrode plaque directly over the right bundle branch in an in vivo canine heart preparation and then recording the activation potentials both during normal conduction and during FRBBB

Methods

Acute experiments were performed in nine mongrel dogs weighing 15 to 30 kilograms anesthetized with 30 mg /kg of phenobarbital Artificial ventilation was maintained according to the Kleinman and Radford nomogram[1] with a Harvard ventilator A thermal blanket was used to maintain body temperature Arterial and venous pressures were monitored throughout the experiment and volume replacement was given to maintain physiologic blood pressures The heart was exposed by a midline sternal incision and the animal was anticoagulated with 10 000 units of heparin The right heart was bypassed by collecting superior and inferior vena caval blood flow into a cardiotomy reservoir and pumping this blood with a roller pump through a blood filter and then into the pulmonary artery A more detailed description of this preparation is described elsewhere[13] With the heart empty of blood a 2 to 3 cm incision was made into the anterior right ventricular wall to expose the septum and the right bundle branch A 10 by 15 mm plaque with 36 stainless steel flush electrodes was then sutured over the right bundle The poles of the electrodes were separated by 1 5 mm across and 3 mm vertically The plaque was positioned just lateral and inferior to the papillary muscle that inserts into the pulmonary conus and was superior and medial to the anterior papillary muscle Up to six simultaneous bipolar electrograms could be monitored down the length of the right bundle at 3 mm intervals After electrode placement the incision in the right ventricular wall was closed and the right heart bypass system was discontinued Right bundle and His electrograms were recorded with a frequency response of 50 to 2 000 Hz ECG leads were recorded at 0 2 to 2 000 Hz Recordings were made on a light beam oscillograph at paper speeds of 25 to 200 cm /sec The sinus node was crushed to allow for slower spontaneous heart rates Driving and premature stimuli were of 2 msec duration and 1 5 times threshold in intensity to the right atrium via bipolar hook electrodes At the termination of each experiment the location of the electrodes were confirmed by staining of the specialized conduction system with iodine solution

Results

FRBBB was produced in nine dogs with high quality recordings from the right bundle branch by the 36-electrode plaque In every case of FRBBB produced the conduction block was found to be located within the first 5 to 6 mm of

From the Nora Eccles Harrison Cardiovascular Research and Training Institute the Cardiology Division Department of Internal Medicine College of Medicine University of Utah, Salt Lake City and the Department of Internal Medicine Albany Medical College of Union College Albany N Y and Albany Veterans Medical Center Albany

Supported in part by Program Project Grant No Hl 13480 and by Research Grant No H? 1.611 from the National Institutes of Health, and by the Richard A. and Nora Eccles Harrison Fund for Cardiovascular Research.

Received for publication Sept. 19 19 9

Accepted for publication Oct 29 1979

Reprint requests Chalmers Lyons, M.D Veterans Administration Medical Center Cardiology Dept Albany N Y 12208

00?-8 03/80/110653 + 04$00 40/0 © 1980 The C V Mosby Co

hypoxic may play a role The change in right bundle size as compared to the left bundle may result in loss of summation effects on conduction

Summary

An in vivo canine heart was prepared by utilizing a temporary right heart bypass system to place close bipolar electrodes along the course of the right bundle branch Activation within the right bundle could be recorded in up to six locations along the right bundle with premature supraventricular stimulation that caused functional right bundle branch block The loss of activation recordings was found to occur in the proximal 0 to 6 mm of the right bundle branch in every instance and in nine different preparations

REFERENCES

1 Lewis T Observations upon disorders of the heart s action Heart 3 279 1912
2 Cohen S I Lau S H Stein E Young M W, and Damato A N Variations of aberrant ventricular conduction in man Evidence of isolated and combined block within the specialized conduction system Circulation 38 899 1968
3 Myerburg R J Gelband H and Hoffman B F Functional characteristics of the gating mechanism of the canine A V conduction system Circ Res 22 1971
4 Myerburg R J Stewart, J W and Hoffman B Electrophysiologic properties of the canine peri A V conducting system Circ Res. 26 361 19
5 Moe G K Mendez C, and Han, J Aberrant propagation in the dog heart A study of functional bundle branch block Circ Res 16 261 19
6 Elizari, M V Greenspan K, and Fisch C Electrophysiological studies in intra ventricular aberrant conduction Adv Cardiol 14 115 19
7 Zipes D P Knope R F Mendez C and Moe G The site of functional right bundle branch block in intact canine heart Adv Cardiol. 14 10 19
8 Damato A N Lau S H Berkowitz, W D R. K M and List, K R Recording of specialized conduction fibers (A V nodal His bundle and right bundle branch) in man using an electrode catheter tech Circulation 39 435 1969
9 Rosen K M Rahimtoola S H Sinno M Z, Gunnar R M Bundle branch and ventricular activation in man A study using catheter recordings of the right bundle branch potentials Circulation 43 1971
10 Lau S H Gustavus B A. and Damato A N Ca recordings and validation of left bundle branch potentials in intact dogs Circulation 42 3 5 19
11 Lyons C J Site of functional right bundle branch block Clin Res 26 603 1978
12 Kleinman L, and Radford. E P Ventilation standards Tidal volume vs body weight and rate Harvard Apparatus Co Inc Dover Massachusetts
13 Lyons C J and Burgess M J Demonstration of re entry within the canine specialized conduction system Am Heart J 98 595 19 9

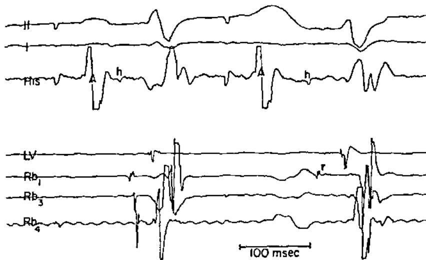


Fig 2 Electrograms are labeled similar to those in *Fig 1* from the same experiment only 1 or 2 minutes later The premature stimulus artifact is now 4 msec more premature There is now functional right bundle branch block with block of activation beyond the most proximal right bundle branch electrode There is delay of activation of the right muscle (compare activation time of right and left ventricular myocardium)

occurred in the proximal portion of the right bundle branch as it emerges onto the surface of the right ventricular septum

Discussion

The occurrence of FRBBB on clinical tracings has generated considerable interest as to the site and mechanism of the conduction block A search for the site of FRBBB has been recently stimulated by the reports of Myerburg and associates[3,4] which utilized an in vitro canine myocardium and showed that the area of the specialized conduction system with the greatest refractoriness was 2 to 3 mm proximal to the Purkinje muscle junction The physiologic role of prolonged refractoriness at the distal specialized conduction system could be consistent with a peripheral conduction block concept Moe and co-workers[5] however have provided indirect evidence suggesting that the site of FRBBB is more proximal Elizari and colleagues were able to show a marked increase in action potential duration in the area of the proximal bundle branches and show slowing of conduction of premature impulses in this area In in vivo canine heart preparations Zipes and associates have shown that the site of block is proximal to the false tendon portion of the right bundle branch Catheter recordings in man [9] and dogs[10] also support a proximal site of FRBBB Our work more precisely documents the site of conduction block to be in the first few mm of the right bundle as it emerges into the right ventricular surface of the septum In none of our experiments was the site of FRBBB located in the middle or distal portions of the right bundle branch Our results also do not lend support to the concept of incomplete right bundle branch block at least in the healthy right bundle with premature stimulation methods The maximum conduction delay prior to complete blockage of conduction was up to 15 msec duration in these studies This is in contrast to the study by Elizari and co workers who noted conduction delays of considerable magnitude using an in vitro preparation The difference in our results may be due to the lack of normal perfusion in their experiments

Our results confirm that the site of FRBBB is in the proximal right bundle branch The possible causes of the conduction block in the proximal right bundle during FRBBB are unknown Several possible mechanisms may be active The change of perfusion from arterial blood to right ventricular cavity blood which is relatively

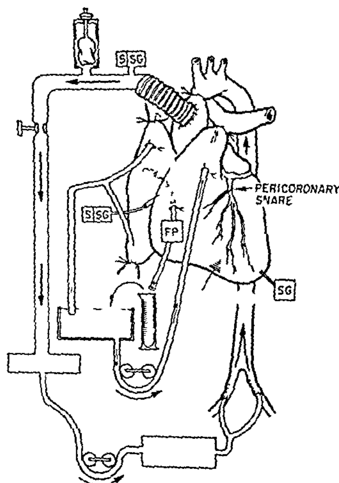


Fig 1 Diagram of the preparation S = sampling site SG = strain gage pressure transducer FP = electromagnetic flow probe

and connected to a Statham P23Db pressure transducer The heart was exposed via a midline sternotomy The internal mammary vessels were ligated bilaterally and the azygous vein the pulmonary artery and the venae cavae were prepared for right ventricular bypass with umbilical tapes placed around each vessel Two Teflon coated stainless steel wire pacing electrodes were introduced about 1 cm apart into the apex of the left ventricle (LV) and were then hooked against the endocardium The electrodes were connected to a battery powered stimulator (Medtronic Inc Model 5807) Complete atrioventricular block was induced by injection of 0 5 to 1 ml of 40 formaldehyde into the region of the AV node The ventricular pacing rate was then set at 120 min

A Satinsky arterial clamp was placed longitudinally on the anterior wall of the ascending aorta proximal to the origin of the brachiocephalic branch A 1.5 cm longitudinal incision was made in the anterior aortic wall, and a 16 m woven Dacron graft was sutured along the incision using two 5-0 Prolene sutures

A segment of the anterior interventricular (anterior descending) branch of the left artery immediately distal to the origin diagonal branch was isolated and a tape snare was placed around it

For right heart bypass as previously described[17 22] the pulmonary artery was cannulated using a No 28F Foley catheter introduced into the vessel via a stab wound conus The superior vena cava was cannulated via the stump of the azygos vein with Bardic cannula and the inferior vena cava cannulated via the right atrial appendage No 32F Bardic cannula The caval venous was drained by gravity into a plastic reservoir The tip of another No catheter was placed in the inflow tract right ventricle For completion of the pulmonary artery was ligated over the catheter (Fig 1)

During right heart bypass drainage bypassed right heart chambers represent nary venous effluent minus LV Thebesian age was diverted through an electromagnetic probe (Micron Instruments Los Angeles) for continuous recording of coronary b

The pressure at the aortic root was by ligating the ascending aorta bet Dacron graft and the origin of the bra alic artery and diverting the entire L (minus coronary blood flow) through th an extracorporeal circuit with a resistance (screw clamp) and capacitance with equal parts of blood and NaCl 0 9 blood was warmed in a heat exchange returned to the animal via cannulas femoral arteries using a second occlusive pump (Cardiovascular Instruments, W Mass) Using this technique the mean arterial pressure ($\overline{SAP}$) was set at 70 during the remainder of the preparation vers

The aortic root pressure was monitored side tube of the systemic circuit using pressure transducer LV pressure and derivative (LV dP/dt) were measured catheter tip pressure transducer (Mill Houston Texas) introduced into the LV

Effect of arterial pressure on left ventricular O consumption, coronary blood flow and reserve capacity following coronary occlusion

William J Bugni M D *
Alexandros C Kralios M D *
Theofilos J Tsagaris M D
Hiroshi Kuida M D
Salt Lake City Utah

There has been considerable interest recently concerning the effects of changes in ventricular afterload on the extent of myocardial injury following coronary artery occlusion Experimental studies suggest that a reduction in ventricular afterload by decreasing coronary perfusion pressure increases ischemic damage following coronary artery occlusion However clinical studies report a decrease in the predicted infarct size if in the course of acute myocardial infarction ventricular afterload is reduced Also studies dealing with the effects of combination therapy with nitroglycerin and phenylephrine on the extent of ischemic injury during acute myocardial infarction have been contradictory Thus there appears to be uncertainty regarding the effects of ventricular afterload changes on the extent of myocardial damage following coronary artery occlusion

The methods commonly employed to assess the extent of myocardial injury involve ST segment mapping and serial analysis of serum CPK changes However recent studies suggest that ST segment changes following coronary artery occlusion may not accurately reflect the magnitude of myocardial ischemic damage Also controversy has arisen concerning the reliability of assessing infarct size from serum CPK changes alone Furthermore these methods assess neither left ventricular functional impairment nor functional capacity of the remaining functional myocardium

The present study was undertaken to evaluate the effect of different mean systemic arterial pressure levels on the reduction of left ventricular functional reserve capacity following the insult of coronary artery occlusion Left ventricular functional reserve capacity was assessed by determining the tolerance of the left ventricle to increasing heart rate and to increasing resistance to ventricular ejection Thus the heart rate and the systemic arterial pressure at which mean atrial pressure attained 12 mm Hg was used arbitrarily to define the limits of left ventricular functional reserve capacity

Materials and methods

Mongrel dogs weighing 18 to 38 kilograms were anesthetized with intravenous sodium pentobarbital (30 mg /kg.) Following intubation with a cuffed endotracheal tube the animals were ventilated using a volume respirator (Harvard Apparatus Co Dover Mass) with 97% O and 3% CO_2 and constant minute ventilation throughout each experiment All animals received a continuous intravenous infusion of sodium bicarbonate 0 05 mM min $^{-1}$ kg $^{-1}$ of body weight for prevention of metabolic acidosis Arterial pressure was monitored from the beginning of the study via a No 8 catheter introduced into the left femoral artery

From the Veterans Administration Medical Center and the Department of Medicine University of Utah College of Medicine Salt Lake City Utah

Supported in part by the Utah Heart Association

Received for publication Oct 10 1979

Accepted for publication Feb 14 1980

Reprint requests A C Kralios, M D Cardiology Section (111A) VA Medical Center 500 Foothill Dr Salt Lake City Utah 84148

Dr Bugni was a Cardiology Fellow

Dr Kralios is a Veterans Administration Clinical Investigator

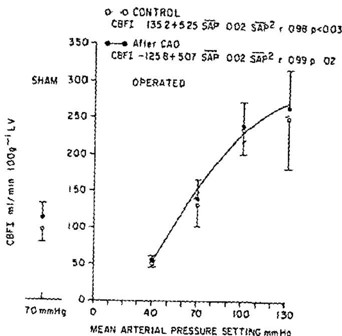


Fig 3 Coronary blood flow index (*CBFI*) changes in response to mean systemic arterial pressure setting before (control) and after coronary artery occlusion (*CAO*) Mean values ± SE for each group of animals (n = 5) Curvilinear relationship of mean values was similar for both conditions

define the lower limits of LVFRC by decreasing $\overline{SAP}$ and HR However when $\overline{SAP}$ was steadily decreased the $\overline{LAP}$ usually decreased in similar fashion Also at slower HR escape ventricular rhythms often intervened preventing substantial decreases in HR Thus data describing the limits of LVFRC for lower $\overline{SAP}$ and HR were not sufficient for statistical analysis

In 25 animals prepared as described control data including assessments of LV functional reserve capacity were obtained Each dog was then randomly assigned to one of five equal groups One group in which $\overline{SAP}$ was maintained at 70 mm Hg served as sham and the coronary artery although similarly prepared was not ligated In the remaining four groups the $\overline{SAP}$ was set at a new level of 40 70 100 or 130 mm Hg After measurement of CBF and MVO_2 at the new pressure setting the previously isolated anterior descending coronary artery was occluded Following coronary occlusion CBF and MVO_2 were determined at 5 minutes 15 minutes and 30 minutes These data were averaged for subsequent statistical evaluation since they did not vary significantly over time After 30 minutes and while the coronary occlusion was maintained the $\overline{SAP}$ was returned to its original control level of 70 mm Hg At this level CBF and MVO[illegible] again determined and LV functional re[illegible] capacity was redetermined by the two techn[illegible] as described

At the end of the experiment the heart [illegible] excised and Evans blue dye was injected [illegible] low pressure into the coronary artery distal to [illegible] ligature Immediately after injection the sta[illegible] LV myocardium was excised and weighed f[illegible] gross estimation of the non perfused LV myo[illegible]dial segment Subsequently the total LV we[illegible] was determined and was used for indexing the [illegible] of the non perfused segment the CBF and MVO_2 thus data obtained both before and a[illegible] CAO were indexed to 100 g of total wet [illegible] myocardium

Statistical analysis was performed using a[illegible] sis of variance for the five groups of data th[illegible] test for paired observations for comparison [illegible] data obtained in each animal before and a[illegible] coronary occlusion and linear or polynom[illegible] regression analysis for estimating regression [illegible] mean data values

Results

There was no significant difference by analy[illegible] of variance in the indexed weight of stained l[illegible] myocardium following actual or sham corona[illegible] ligation (Table I) The mean percent for all [illegible] dogs was 27 6 ± 1 0 of total LV myocardium

Myocardial oxygen consumption ind[illegible] (MVO_2I) values before and after coronary occ[illegible] sion for the four groups in which the left ante[illegible] interventricular coronary artery was ligated, [illegible] not differ significantly by the t test for pa[illegible] observations (Table II) In the sham opera[illegible] group this MVO_2I difference was significa[illegible] MVO I mean values bear a linear relations[illegible] the $\overline{SAP}$ setting both before and after coron[illegible] occlusion (Fig 2) Since neither regression slope[illegible] nor y intercepts differed significantly the com[illegible] mon predictive equation derived is

MVO_2I ml O_2/min 100 g⁻¹ LV =

2 71 + 0 103 $\overline{SAP}$ mm Hg $r = 0\ 99$ $p < 0\ 00$[illegible]

Coronary blood flow index (CBFI) va[illegible] before and after coronary occlusion did not d[illegible] significantly in any of the experimental gro[illegible] (Table II) CBFI mean values bear a sim[illegible] curvilinear parabolic relationship to the [illegible] both before and after coronary occlusion (Fi[illegible] The predictive quadratic equation derived f[illegible] values is

apex The pressure signal of the catheter tip transducer was matched with the pressure signal obtained via the lumen using a conventional P23Db pressure transducer A No 8 catheter was placed in the left atrium (LA) via the LA appendage and pressure was monitored using a P23Db transducer Zero pressure reference was set at the mid right atrial level for all transducers

A fiberoptic catheter was placed in the proximal coronary sinus via the right atrial appendage and was connected to an In Vivo oximeter (Physio Control Seattle Wash) for continuous monitoring of oxyhemoglobin saturation of coronary sinus blood and for periodic blood sampling

The mean ($\overline{SAP}$) and phasic aortic pressure the left ventricular pressure (LVP) the coronary blood flow (CBF) signal the coronary sinus oxygen saturation ($ScsO_2$) signal a vertical body surface ECG lead and the LV dP/dt were recorded using an oscillographic recorder (Honeywell 1612 Denver Colo) The temperature of the animals as measured directly from the posterior surface of the heart was maintained at 36 8 ± 0 2 C through adjustment of warm water flow through the heat exchanger

The flowmeter signal of coronary blood flow (CBF) was calibrated before each determination by repetitive (five to eight) timed collections (30 seconds) of the continuous siphon drainage of the right ventricle

Blood samples were obtained from the arterial circuit and from the coronary venous drain and were iced immediately for determination of O_2 content by the Van Slyke method [11] The pH pO and pCO_2 of blood samples were determined using the Astrup apparatus The hemoglobin concentration of the samples was also determined Myocardial oxygen consumption (MVO_2) was derived as the product of the CBF and the corresponding arteriovenous oxygen difference and was then indexed to 100 g of total LV myocardium (MVO_2I) Wet LV weight was determined at the conclusion of the experiment after excision of atria along the atrioventricular groove and the right ventricle along its attachment to the interventricular septum

Experimental protocol *Left ventricular functional reserve capacity* (LVFRC) testing was conducted as follows

1 With the HR set at 120 min the resistance of the arterial extracorporeal circuit was gradually increased at a constant rate by tightening the screw clamp thereby increasing the $\overline{SAP}$ until the mean LA pressure ($\overline{LAP}$) rose to at least 14 mm Hg but not more than 16 mm Hg The slope of $\overline{SAP}$ versus $\overline{LAP}$ was then derived by linear regression analysis of corresponding data points and the $\overline{SAP}$ at which the $\overline{LAP}$ attained 12 mm Hg was designated as the pressure limit of the LVFRC

2 With the $\overline{SAP}$ set and maintained at 70 mm Hg the ventricular pacing rate was steadily increased until the $\overline{LAP}$ rose to the above values The slope of the HR versus $\overline{LAP}$ was similarly derived and the HR at which the $\overline{LAP}$ attained 12 mm Hg was designated as the HR limit of the LVFRC

In each experiment attempts were made to

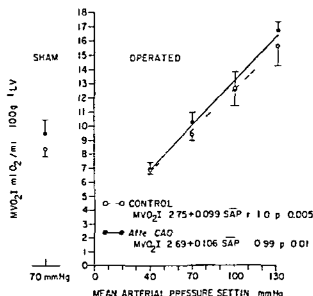


Fig 2 Myocardial O consumption index (MVO I) changes in response to mean systemic arterial pressure setting before (control) and after coronary artery occlusion (*CAO*) Mean values ± SE for each group of animals (n = 5) Linear relationship of mean values was similar for both conditions.

Table I Estimated percent of non perfused LV myocardium following coronary artery occlusion in each five animal group

Mean systemic arterial pressure setting during coronary artery occlusion (mm Hg)					
40	70	100	130	70 (Sham)	p
26 6 ± 1 7	30 8 ± 1.9	24.2 ± 1 4	25 6 ± 2.7	30 7 ± 2.2	NS

p = Derived by analysis of variance

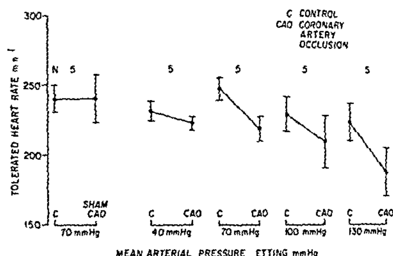


Fig 5 Tolerated heart rate resulting in mean left atrial pressure of 12 mm Hg before (control) and after minutes of coronary artery occlusion (CAO) at the indicated mean systemic arterial pressure setting Tolerated heart rate range after CAO is not significantly affected by the level of pressure setting. However the mean values of tolerated heart rate bear a negative relationship (r = 0 95) to the pressure setting

Before coronary occlusion the results of the control assessment of LV functional reserve capacity as tested by increasing HR, did not differ among the five groups (Fig 5) For all 25 dogs the mean HR at which the $\overline{LAP}$ attained 12 mm Hg was 234.5 ± 4 6 min

Following 30 minutes of coronary occlusion in the four groups with coronary ligation $\overline{LAP}$ of 12 mm Hg was attained during LV functional reserve capacity testing at a HR which was lower than control by an average of 23 1 ± 4 7 min (p < 0 001) (Fig 5) Although the magnitude of this reduction was not significantly different among the four groups by analysis of variance there was a slight trend (0 4 min ¹ per mm Hg) for the mean group values of these post occlusion estimates to correlate negatively with the $\overline{SAP}$ setting of the group In the sham group the results of the control and post sham occlusion evaluations of LV functional reserve capacity by HR did not differ

Discussion

Critique of method The criterion of 12 mm Hg of left atrial pressure for defining the limits of LV functional reserve capacity was set arbitrarily however Braunwald and colleagues[5] reported this to be the upper limit of normal for resting humans Furthermore in these and in similar previous experiments we observed that when $\overline{LAP}$ reaches this level as a result of rapid heart rate systemic arterial pressure increase or coronary artery ligation its rate of rise is abrupt leading to rapid deterioration of ventricular function

We utilized changes in heart rate and arterial pressure to test LV functional reserve capacity because such changes can be controlled independently A similar approach using changes in HR and afterload was used previously by several investigators in both the clinical and experimental setting[16] Quinones and colleagues[6] employed changes in preload in addition to changes in HR and afterload to achieve the same goal

Although it has been adequately demonstrated that after deprivation of blood supply depression of myocardial contractile function occurs within seconds[29,30] the time for retesting LV functional reserve capacity following coronary artery occlusion was set at 30 minutes We elected permanent coronary ligation instead of the coronary occlusion-release model because the latter although probably more sensitive in depicting effects of hemodynamic alterations involves only transient hypoxia We felt pertinent to the purposes of this study that 30 minutes represented sufficient time for the ischemic tissue and vasculature to be affected by the systemic arterial pressure setting with its opposing effects on O_2 supply and demand afforded by the systemic arterial pressure set point either in the direction of preservation of function although not necessarily determining long term tissue viability

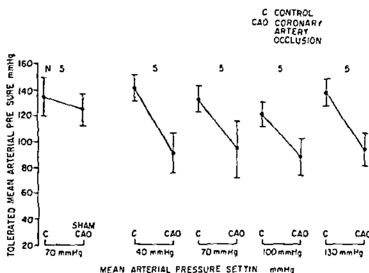


Fig 4 Tolerated mean systemic arterial pressure in mm Hg resultin in mean left atrial pressure of 12 mm Hg before (*control*) and after 30 minutes of coronary artery occlusion (*CAO*) at the indicated mean systemic arterial pressure setting. Tolerated pressure after CAO is not affected by the level of pressure setting

Table II Myocardial oxygen consumption and coronary blood flow indices before and after coronary artery occlusion

	Mean systemic arterial pressure setting during coronary artery occlusion (mm Hg)				
	40	*70*	*100*	*130*	*70 (Sham)*
MVO I					
(mL O_2/min 100 g LV)					
Control	6 90 ± 0 26	9 48 ± 0 53	12.64 ± 1 17	15 79 ± 1 44	8 35 ± 0 60
Post coronary artery occlusion	6 99 ± 0 39	10 30 ± 0 65	12 66 ± 1.20	16 82 ± 0 60	9 49 ± 0 91
Mean difference	0 10 ± 0 34	0 85 ± 0 "	0 0? ± 0 47	1 03 + 0 98	1 14 ± 0.3?
p	NS	NS	NS	NS	< 0 05
CBFI					
(ml /min 100 g LV)					
Control	52 8 ± 5 5?	131 7 ± 30 0	234 9 ± 33 6	252 2 ± 68 0	97.3 ± 16 5
Post coronary artery occlusion	54 5 ± 4 6	140 2 ± 26	238 8 ± 34 3	266 8 ± 51 6	113 4 ± 18 7
Mean difference	3 4 ± 3 2	8 5 ± 3 4	3 9 ± 7.2	14 6 ± 16 6	16 04 ± 3.8
p	NS	NS	NS	NS	< 0 01

Determined by paired t test

CBFI ml /min 100 g LV =
$-130\,0 + 5\,16\,\overline{SAP}$ mm Hg $- 0\,016\,\overline{SAP}$ mm Hg

or $\overline{SAP}$ within 40 to 100 mm Hg the relationship appears linear and the predictive equation is
CBFI ml /min 100 g LV =
$-70\,2 + 3\,03\,\overline{SAP}$ mm Hg $r = 0\,99$ $p < 0\,001$

Before coronary occlusion control LV functional reserve capacity estimates assessed by increasing aortic root pressure did not differ significantly among the five groups by analysis of variance (Fig 4) For all 25 animals the average $\overline{SAP}$ at which the $\overline{LAP}$ attained 12 mm Hg prior to coronary occlusion was 130 4 ± 6.2 mm Hg After 30 minutes of coronary occlusion in the four groups in which the left anterior interventricular coronary artery was ligated $\overline{LAP}$ of 12 mm Hg was attained during LV testing at a $\overline{SAP}$ level which was significantly lower than control However the magnitude of this reduction in all four groups was similar by analysis of variance averaging 41 9 ± 6 2 mm Hg ($p < 0\,001$) (Fig 4) In the sham group the results of the control and post sham occlusion did not differ

dogs [17 - 23] Nakano[37] reported findings similar to ours in anesthetized dogs but the uncontrolled cardiac output in that study decreased drastically as a result of tachycardia It should be stated however that in preparations with fixed cardiac output stroke volume bears an inverse relationship to HR and according to previous findings from this laboratory the workload imposed on the LV as judged by MVO_2 measurements is about one fifth of that imposed with HR increases at constant stroke volume [38] It is therefore conceivable that different results in conscious dogs may at least in part reflect changes in cardiac output during rapid pacing

With the assumption that loss of LV functional reserve capacity bears a directional although not necessarily linear relationship to the functional loss of myocardium the results of this study clearly indicate that systemic arterial pressure setting does not affect the extent of loss of functioning myocardium following coronary artery occlusion Previous studies using electrophysiological or enzymatic correlates supported mutually opposing views [6] Recently Wyatt and co workers [4] in preparations with left anterior descending stenosis suggested that increasing afterload may have beneficial effects on myocardial metabolism but detrimental effects on ventricular function concluding that ischemic injury may be reduced by increasing arterial pressure but at the expense of LV function Obviously results are bound to vary first according to the degree of stenosis which determines maximal coronary blood flow second according to the level and increment of arterial pressure which determine coronary blood flow and LV work and third according to the oxygenation of arterial blood Our data (Figs 2 and 3) may provide some insight on the effect of systemic arterial pressure changes on the balance of myocardial O supply and demand Arterial pressure bears a linear relationship to MVO_2 but curvilinear to CBF so that for pressure levels above 100 mm Hg the ratio of O supply over demand becomes progressively less favorable The average slope of MVO I increase in response to systemic arterial pressure increments is 0 103 ml O_2 per mm Hg On the other hand for normal blood O_2 carrying capacity of 20 vol % O_2 supply within the 40 to 100 mm Hg pressure range is about three times steeper but above 100 mm Hg tends to plateau towards the MVO I slope Obviously in the presence of coronary stenotic lesio or lower O_2 carrying capacity the O curve will be depressed accordingly Th indicate that an optimal relationship of O to demand relationship occurs at about Hg Increase above as well as decrease be level may have a potentially detrimenta

The reduction of tolerance to tachyca lowing coronary occlusion did not diffe groups with different $\overline{SAP}$ setting How trend toward negative correlation of mea of tolerated HR with $\overline{SAP}$ settin small may warrant further investi both tachycardia [6 41] as well as ischemia result in incomplete myocardial relaxati

The criteria of heart rate and arterial used in this experimental study for estim functional reserve capacity represent th correlates by which survival and degree o ity are ultimately determined Althou term effects may differ it appears acc the results of this study that systemic pressure setting at the early state of ac cardial infarction is not an important nant of functional and probably anatom of myocardium However since mean arterial pressure levels of about 100 afford the best O_2 supply to-demand r pressure level may be optimal for reg compromised perfusion

Summary

The effect of mean systemic arterial ($\overline{SAP}$) on myocardial O_2 consumption coronary blood flow (CBF) and the redi left ventricular (LV) reserve capacity from coronary artery occlusion was stud open chest pentobarbital anesthetized d fixed cardiac output and controlled he (HR) and $\overline{SAP}$ In all animals baseli and CBF were obtained and LV reserve was determined by identifying the HR level which raised mean left atrial pres mm Hg After uniform placement of a nary snare the dogs were randomize equal groups and $\overline{SAP}$ was set at 40 groups) 100 and 130 mm Hg MVO were redetermined and the coronary ar ligated in all except one group (70 mm H served as sham control Thirty minut coronary occlusion MVO CBF and LV capacity were determined again Percent

The basic assumption in this study is that ormally LV functional reserve capacity is a leasure of maximal functioning of all LV seg ients Therefore loss of functional contribution f any of the segments would be reflected as a eduction of the total LV functional reserve revious work supports this rationale although ot necessarily in the sense of a simple mathe iatical relationship[3, 33]

While only one complete sham group for the 70 im Hg pressure setting was provided in this udy other sham experiments performed at both ie 70 and the 130 mm Hg pressure settings iowed that pressure setting did not modify the stimates of LV functional reserve capacity efore or after sham coronary artery occlusions ince the pressure setting alone did not appear to ave an independent effect on LV functional eserve capacity estimates the observed decre ients after coronary artery occlusion were attri uted exclusively to the functional loss of myo ardium Several aspects in the design of this tudy were different from those of previous stud es,[6, 7, 40] and might have contributed to different esults (1) complete coronary occlusion instead f stenosis was utilized (2) left ventricular output ras kept constant rather than allowed to vary in esponse to rate and pressure increases (3) the rterial bypass extracorporeal circuit was proba ly stiffer than the normal arterial tree thereby r higher actual workload to the left ventricle may ave been imposed for comparable mean arterial ressure settings

Discussion of results The grossly estimated ize of non perfused LV myocardium resulting om the coronary artery occlusion was substan ial but uniform among groups This may reflect niformity of occlusion successful randomiza ion but also to some extent the constancy of the ontrolled variables Accordingly differences in V functional reserve capacity among groups ould not be attributed to non uniformity of oronary artery occlusion

Previous work from this laboratory indicated hat left ventricular efficiency does not change fter coronary artery ligations which result in a wide range of sizes of ischemic myocardium[3] In his study constancy of MVO_2 before and after oronary ligation in each group with different ystemic arterial pressure setting implies that fficiency of the intact myocardium also remains onstant at different levels of LV workload The MVO_2 constancy is also indicative of the stability of preparations following coronary occlusion Control MVO_2I values in the sham group were somewhat but not significantly lower than those of the experimental group operated at 70 mm Hg therefore values after sham coronary occlusion appeared higher than sham control

The linear relationship of MVO_2I versus mean systemic arterial pressure setting (Fig 2) was similar before and after coronary occlusion affecting up to 27% of LV mass This further supports the notion that total left ventricular O consumption is proportional to workload and independent of relative size of intact or ischemic myocardium[34] Similar findings supporting the independence of total left ventricular O con sumption from the perfusion or oxygenation con ditions of the myocardium were previously reported in preparations in which MVO_2I require ments were modified by means of heart rate changes before and after coronary occlusion[35]

These findings indicate that for similar work load the reserve capacity of the myocardium is able to compensate for the functional loss of ischemic myocardium without change in O cost In other words left ventricular efficiency remains unchanged at all levels of function although the work per gram of functioning myocardium varies On this basis the extent of functional loss of myocardium cannot be assessed by MVO_2 mea surements as long as the loss is compensated by the functional reserve of the intact part Left ventricular decompensation obviously will occur when the capacity of the intact part to consume O_2 and produce energy is exhausted It follows logically that the larger the size of the remaining intact part the higher the energy demands the ventricle can handle before decompensation Con versely the larger the size of functionally lost tissue the lower the tolerance to increased demands However because of the possibility that the functionally lost tissue not only ceases con tributing but may actually dissipate energy larger infarcts may impinge upon LV functional reserve capacity out of proportion to their size

During the control testing of LV functional reserve capacity $\overline{LAP}$ of 12 mm Hg was attained at the rather low mean systemic arterial pressure level of 130 ± 6 8 mm Hg This level however is in accord with previous reports[35, 3] In regard to heart rate response previous studies reported a lower tolerance of heart rate in intact conscious

after coronary artery occlusion Ann Intern Med 31 429 1949
31 Harnarayan C Bennett M A., Pentecost B L and Brewer D B Quantitative study of infarcted myocardium in cardiogenic shock Br Heart J 32 728 1970
32. Page D L. Caulfield J B Kastor J A De Sanctis R W., and Sanders C A Myocardial changes associated with cardiogenic shock N Engl. J Med 285 133 1971
33 Pairolero P C McCallister B D Hallermann F J and Ellis H Experimental production and hemodynamic effects of left ventricular akinesis Am J Cardiol. 25 120 1970
34 Kralios A. C., Tsagaris T J., and Kuida H Myocardial oxygen consumption after major coronary artery occlusion in anesthetized dogs with constant left ventricular workload, Cardiovasc Res 10 642 1976
35 Goodyear A. V N Goodkind M J., and Landry A B Ventricular response to a pressure load Circ Res 10 885 1962
36 Tsakiris A G., Donald D E., Rutishauser W J Banchero N and Wood E H Cardiovascular responses to hypertension and hypotension in dogs with denervated hearts, J Appl. Physiol. 27 817 1969
37 Nakano J Effects of atrial and ventricular tachycardias on the cardiovascular dynamics Am J Physiol 206 547 1964
38 Kralios A C Tsagaris T J and Kuida H Comparison of rhythm and rate induced myocardial O[illegible] changes before and after coronary occlusion, [illegible] J 96 372 1978
39 Killip T., III and Kimball, J T Treatment [illegible] dial infarction in a coronary care unit A [illegible] experience with 2[illegible]0 patients, Am J Card[illegible] 1967
40 Wyatt H L., Da Luz, P L., Waters, D D [illegible] C and Forrester J S Contrasting influence[illegible] tions in ventricular preload and afterload up[illegible] hemodynamics function and metabolism [illegible] myocardium Circulation 55 318 1977
41 Mitchell J H Linden R J and Sar[illegible] Influence of cardiac sympathetic and vagal [illegible] lation on the relation between left ventric[illegible] pressure and myocardial segment length, [illegible] 8 110 1960
42. McLaurin L. P., Grossman W and He[illegible] Defective left ventricular relaxation during e[illegible] myocardial ischemia (Abstr) Clin Res. 23 [illegible]
43 Mathey D Bleifeld W and Franken G L[illegible] ular relaxation and diastolic stiffness in [illegible] myocardial infarction Cardiovasc Res. 8 58[illegible]
44 Barry W H Brooker J Z., Alderman, [illegible] Harrison D C Changes in diastolic stiffness [illegible] the left ventricle during angina pectoris, [illegible] 49 255 1974

IMPORTANT
INFORMATION FOR AUTHORS

All manuscripts for the AMERICAN HEART JOURNAL should be sent to

Dean T Mason M D
Section of Cardiovascular Medicine
University of California
School of Medicine
Davis California 95616

erfused myocardium did not differ among groups 27 6 ± 1%) MVO_2 bore a linear relationship to SAP setting whereas CBF bore a curvilinear elationship Coronary occlusion did not modify hese relationships Significant but similar decreases in tolerated HR (23 1 ± 4 7 min) and SAP (41 9 ± 6 2 mm Hg) from control values vere observed in all four groups regardless of SAP etting

We concluded that the impact of coronary igation on MVO CBF the loss of functional *reserve capacity and possibly the extent of* ischemic injury of the left ventricle is not modi ied by afterload changes However optimal O_2 upply to demand ratio appears at SAP of about 00 mm Hg

EFERENCES

1. Maroko P R and Braunwald E Modification of myocardial infarction size after coronary occlusion Ann Intern Med 79 720 1973
2. Maroko P R Kjekshus J K Sobel B E Watanabe T., Covel J W Ross, J Jr and Braunwald E Factors influencing infarct size following experimental coronary artery occlusions Circulation 43 67 1971
3. Shell, W E and Sobel B E Protection of jeopardized ischemic myocardium by reduction of ventricular after load N Engl. J Med 291 481 1974
4. Chianello M Gold H K Leinback R C Davis M A and Maroko P R Comparison between the effects of nitroprusside and nitroglycerin on ischemic injury during acute myocardial infarction Circulation 54 766 1976
5. Borer J S Redwood D R Levitt B Cagin N Bianchi C Vallin H and Epstein S E Reduction in myocardial ischemia with nitroglycerin or nitroglycerin plus phenylephrine administered during acute myocardial infarction N Engl. J Med 293 1008 1975
6. Come P C., Flaherty J T., Baird M G Rouleau J R Weisfeldt M L Greene H L Becher L and Pitt B Reversal by phenylephrine of the beneficial effects of intravenous nitroglycerin in patients with acute myocardial infarction N Engl J Med 293 1003 1975
7. Maroko P R Lilley P., Covell J W Sobel B E Ross J Jr and Braunwald E Precordial ST segment elevation mapping An atraumatic method for assessing alterations in the extent of myocardial ischemic injury The effects of pharmacologic and hemodynamic interactions Am J Cardiol 29 223 1972
8. Shell, W E Kjekshus J K and Sobel B E Quantitative assessment of the extent of myocardial infarction in the conscious dog by means of analysis of serial changes in serum creatine phosphokinase activity J Clin Invest. 50 2614 1971
9. Smith H J Singh, B N Norris, R M John M B and Hurley P J Changes in myocardial blood flow and ST segment elevation following coronary artery occlusion in dogs, Circ Res 36 697 1975
10. Irvin, R G and Cobb F R Relationship between epicardial ST segment elevation regional myocardial blood flow and extent of myocardial infarction in awake dogs, Circulation 55 825 1977
11. Thompson P F and Katavatis V Acute myocardial infarction Evaluation of precordial ST segment mapping Br Heart J 38 1020 1976
12. Roe C R and Starmer C F A sensitivity analysis of enzymatic estimation of infarct size Circulation 52 1 1975
13. Kralios A C Tsagaris T J and Kuida H Myocardial oxygen consumption at constant left ventricular work load and varying arterial oxygenation Cardiovasc Res. 9 811 1975
14. Van Slyke D D., and Neil J M Determination of gases in blood and other solutions by vacuum extraction and manometric measurement J Biol Chem 61 523 1927
15. Braunwald E Brockenbrough E C., Frahn C J and Ross J Jr Left atrial and left ventricular pressures in subjects without cardiovascular disease Circulation 27 267 1961
16. Pasternac A Gorlin R., Sonnenblick E H Haft J I and Kemp H G Abnormalities of ventricular motion induced by atrial pacing in coronary artery disease *Circulation* 45 1195 1972
17. Tomoike H Franklin D and Ross, J., Jr Detection of myocardial ischemia by regional dysfunction during and after rapid pacing in conscious dogs Circulation 58 48 1978
18. Parker J O Ledwick J R West R O and Case R B Reversible cardiac failure during angina pectoris Circulation 39 745 1969
19. Linhart J W Hildner F J Barold S S Lister J M and Samet, P Left heart hemodynamics during angina pectoris induced by atrial pacing Circulation 40 483 1969
20. Lau S H Cohen S I Stein E Haft J I., Kinney M J Young M W Helfant R H and Damato A N Controlled heart rate by atrial pacing in angina pectoris Circulation 38 711 1968
21. Pasyk S Flameng W., Wusten B and Schaper W Influence of tachycardia on regional myocardial flow in chronic experimental coronary occlusion Basic Res Cardiol 71 243 1976
22. Neill W A Oxendine J Phelps, H., and Anderson R P Subendocardial ischemia provoked by tachycardia in conscious dogs with coronary stenosis Am J Cardiol 35 30 1975
23. Hutton I Platt, M Watson J., Templeton G and Willerson J Influence of frequency of atrial contraction on coronary blood flow and ventricular performance in the conscious dog with myocardial infarction Cardiovasc Res. 10 109 1976
24. Domeneck R. J and Goick J Effect of heart rate on regional coronary blood flow Cardiovasc Res. 10 224 1976
25. Pitt B and Gregg D E Coronary hemodynamic effects of increasing ventricular rate in the unanesthetized dog Circ Res. 22 753 1968
26. Quinones, M A., Gaasch W H., and Alexander J K Influence of acute changes in preload, afterload contractile state and heart rate on ejection and isovolumic indices of myocardial contractility in man Circulation 53 292 1976
27. Ross, J and Braunwald E The study of left ventricular function in man by increasing resistance to ventricular ejection with angiotensin Circulation 29 739 1964
28. Downing F E., and Sonnenblick E H. Effects of continuous administration of angiotensin II on ventricular performance J Appl Physiol 18 585 1963
29. Tennant R., and Wiggers, C J The effect of coronary occlusion on myocardial contraction Am. J Physiol 112 351 1935
30. Prinzmetal M Schwartz L. L. Corday E., Spritzler R Bergman H C., and Kruger H E Studies on the coronary circulation VI loss of myocardial contractility

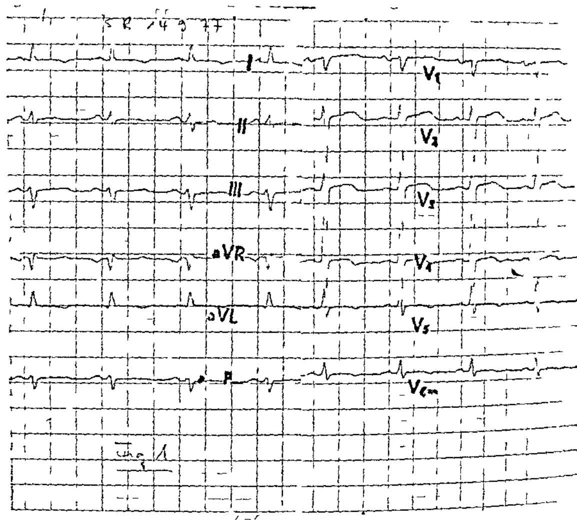


Fig 1 ECG on admission (see text)

dia (104/minute) a distinct pretibial edema enlargement of the heart on percussion splitting of the second heart sound and a soft systolic murmur at the apex on auscultation The blood pressure was 140/80 mm Hg and the jugular venous pressure was not raised

The electrocardiogram (Fig 1) showed a sinus tachycardia marked left axis deviation (greater than −45 degrees) resembling a left anterior hemiblock, minimally el vated convex ST segments terminally negative T waves in Leads I II aV_L and V On x ray (Fig 2) there was a cardiomegaly involving all chambers The heart volume measured by the method of Musshoff and Reindell was 1 030 ml or 15 6 ml/kg weight In addition there were moderate signs of pulmonary congestion The echocardiogram showed enlargement of the left ventricle with diminution of left posterior wall motion There was no pericardial fluid

The results of the laboratory studies are summarized below Erythrocyte sedimentation rate was 103 mm in the first hour white cell count was 9 200/mm plasma thyroxin was 7 1 µg % plasma triiodothyronine was 104 µg % antistreptolysin titre was below 200 I U rheumatoid factor was negative antistreptolysin O reaction 50 U /ml antistreptodornase B was 1 50 antihyaluronidase was 1 < 700 anti NADase was 1 < 50 antistaphylolysin reaction was 1 0 U/ml and CRP was negative Titers for influenza A influenza B param[illegible] Epstein Bar virus and Q fever were negative [illegible] was observed Antinuclear antibodies were not detected

During the course of the disease (Table I) compl[illegible] fixing antibody titers rose from 1 < 16 (one week [illegible] of symptoms) to 1 256 (three weeks after onset) [illegible] virus (CMV) was isolated from the urine taken [illegible] onset of symptoms Specific IgM antibodies were d[illegible] the first serum specimen (first week titer 1 1 024) and [illegible] declined to the end of the third week (1 64)

The technic for the detection of IgM antibodies has be[illegible] described in detail elsewhere[11] the indirect im[illegible] cence method was employed, using CMV infected [illegible] fibroblasts as a source of antigen and fluorescein [illegible] globulin fraction against human µ-chains (d[illegible] rabbit origin)

For the detection of complement fixing antibodies [illegible] extracted antigen (Behring Werke Marburg W Ger[illegible] was used Virus isolation was carried out on human [illegible] cells

After three weeks bed rest the signs of heart [illegible] disappeared On discharge the electrocardiogram [illegible] normal (Fig 3) and the heart volume by [illegible] decreased to 710 ml or 10 6 ml/kg and was [illegible]

;ase reports

ytomegalovırus myocardıtıs

Wınk M D
ıı Schmıtz M D
eıburg/Br West Germany

r

ɜytomegalovırus ınfectıon ıs extremely frequent (owever clınıcal manıfestatıons are rare Thus ın Western Europe and ın the USA 50 to 60% of dults[60] ın Great Brıtaın about 55%[53] and ın weden 90 to 100% of persons over the age of 65 how evıdence of past ınfectıon There was an ıfectıon rate ın the newborn of 33% to 75% the ıte decreased to 29% durıng the fırst year and ın dults an ıncıdence of 35%[18] was observed In reıburg (W Germany) the ınfectıon rate ın the rst sıx month of ınfancy was 20% to 30% This ıcıdence dıd not change ın subsequent chıldhood ntıl the perıod between 15 and 30 years when ıere was a second ıncrease of the ıncıdence to 3% to 70% It ıs lıkely that after a subclınıcal ıfectıon the mother transfers the cytomegalovı ıs to the fetus which may lead to ıntra terıne death or prenatal ınfectıon wıth cere ral or vısceral ınjurıes[5 35 60] The perınatal nd early postnatal ınfectıons are not dıstınctly parable from the vısceral form of the prenatal ıfectıon The ınfectıon of the older chıld and dult are acquıred ıllnesses Frequently a benıgn patıtıs[2 6 7 5] ıs observed but evıdence of ırther systemıc ınvolvement such as heterophıl gatıve ınfectıous mononucleosıs[32] or olyneurıtıs of the Guıllaın Barre type and Fısher ndrome[25 2 8 31] autoımmune hemolytıc ıemıa[63] splenomegalıes anorexıa and ul ra but also ınflammatıon of the lungs kıd ys adrenals the vagına and other or ıns[6 2 7 5] have been reported

om the Department of Medı ın Dıvısıon of Clını al Cardı logy ıd th Dep rtment of Bacterıology Unıversıty of Freıburg Fre burg Germany

eceıved f publ c t on N 15 1978
cepted fo publıcatıon June 28, 1979

eprınt requests K Wınk M.D Dept. of Medı ıne, Dıvısı n of ınıc I Cardı l gy Unıversıty of Freıburg, Freıburg, W Germ ny ugstetterstr 55

Table I Vırologıcal dates ın the course of the dısease

	1 week after ons t	*14 days after onset*	*3 weeks after onset*
Complement fıxıng antıbodıes	1 16	n g	1 256
IgM antıbodıes	1 1024	neg	1 64
CMV from urıne	–	+	–

neg = neg tıve

Observatıons of alteratıons of the heart ın cytomegalovırus ınfectıon are comparatıvely rare[3 5 5] Wılson Morrıs and Rees de scrıbed a female patıent, aged 60 years wıth a sıgnıfıcant rıse ın cytomegalovırus complement fıxıng antıbody who became ıncreasıngly breath less and had repeated attacks of paroxysmal dyspnea after a head cold which progressed to dry cough and wheezıng On clınıcal examınatıon she was obvıously ıll febrıle (38.2° C) and dyspneıc at rest The jugular venous pressure was raısed 5 cm above the sternal angle There was gallop rhythm wıth pansystolıc and mıd dıastolıc mur murs at the apex and also fıne rales at both lung bases The electrocardıogram showed sınus tachy cardıa left bundle branch block and left ventrıc ular hypertrophy the chest x ray demonstrated cardıomegaly and pulmonary congestıon

Because a cytomegalovırus myocardıtıs ıs rare we felt justıfıed ın reportıng a comparable patıent of our own

Case report

One week before hıs admıssıon to hospıtal, a prevıously healthy man aged 31 years, became progressıvely breathless on effort, needıng to rest after goıng up one flıght of staırs. Moreover he notıced swellıng of hıs ankles and legs. He had nocturıa three tımes each nıght.

Prevıously no cardıac abnormalıtıes had been detected. The patıent presented wıth low grade fever (37.5 C) a tachycar

002-8 03/80/110667 + 06$00 60/0 © 1980 The C V Mosby Co

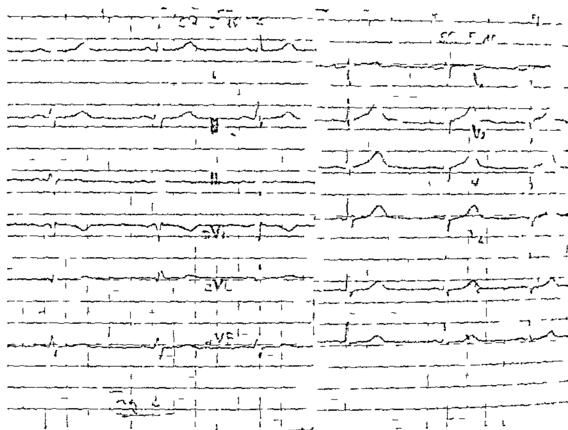


Fig 3 ECG on discharge (see text)

complement fixing antibodies from 1 < 8 to 1 > 64 At necropsy the heart was enlarged and weighed 515 g The microscopic examination showed foci with lymphocytic infiltration and focal fibrosis No inclusion bodies could be seen The pericardial sac contained 180 ml of hemorrhagic fluid so that the question arises whether there was a hemorrhagic tamponade of the heart following the heparin treatment of the coagulopathy

The role of drug treatment of cytomegalovirus infections is unclear Idoxuridine has been effective in infections with the herpes virus[4 52] to which group of viruses the cytomegalovirus also belongs This drug was also used in cytomegalovirus infection with success defined as clinical improvement as well as lowering at the urine content of viruses[6] Floxuridine and 5 fluorodeoxyuridine seemed to have a favorable effect on patients with cytomegalovirus pneumonia and seemed to shorten the clinical course if they were also combined with prednisolone [6] The successful use in generalized herpes infection of cytosine arabinoside hydrochloride[79] a newer antiviral agent led Wilson Morris and Rees[6] to at[illegible] its application in their patient with cytome[illegible] rus myocarditis but only a fall in the [illegible] venous pressure accompanied by a fall in viral titer were observed Their patient has [illegible] remained symptom free on a strict regimen [illegible] persisting gallop rhythm mitral in[illegible] murmur left bundle branch block and ca[illegible] megaly

In view of the many potential toxic side e[illegible] of the above mentioned viricidal drugs t[illegible] probably should be used with restraint and [illegible] conservative means of therapy applied to o[illegible] viral forms of myocarditis such as prolonged [illegible] rest digitalis diuretics etc should be [illegible] considered for these patients

Prophylaxis by the development of vacc[illegible] techniques is now being investigated [illegible] techniques is now being investigated [illegible] clinical application of these techniques [illegible] justified [1]

Summary

A male patient aged 31 years, with a cytome[illegible] lovirus (CMV) myocarditis is described [illegible]

ormal limits (Fig 4) Also the echocardiogram showed no athologic findings The ESR normalized to 7 mm There ave been several reexaminations of the patient to the date of porting none of which have shown signs of recurrence

iscussion

The diagnosis of cytomegalovirus infection has een improved in recent years because of the evelopment of laboratory methods for determi ation of different cytomegalovirus immunglobu ns (IgG IgM IgA) by immunfluorescence[49 5] herefore the diagnosis of a fresh infection is not pendent on the laborious virus isolation [2] he presence of virus specific IgM antibodies pecially seems to be very helpful for diagnosis of cent CMV infection In our case reported here e were able to detect

1 a cytomegalovirus IgM antibody titer of > 64

2 a fourfold increase in the titer of comple ent fixing antibodies and

3 virus isolated from urine

hus a recent CMV infection is supported by veral diagnostic parameters

In the older child and in the adult the appear nce of IgM antibodies is a reliable sign of an tive process[20 1] even if relatively low KBR ters of 1 16 are found[3] Usually the IgM anti odies will also be eliminated from the serum veral months after the infection[5] and therefore ill have a great diagnostic significance

The IgG antibodies however may be demon rable for years[23] and therefore serve as a sign of past infection In the isolation of the virus from rine care must be taken to avoid rapid inactiva on of the virus at room temperature and there re the specimen must be quickly transported to e virology laboratory

Cytomegalovirus infection is frequently asso ated with other severe conditions such as leu emia malignant lymphoma lymphogranuloma yocardial infarction pneumonia fungus infec on liver abscess toxoplasmosis sepsis miliary iberculosis or other debilitating condi ons[8 8 45 58] or appears after cytostatic mmunsuppressive and corticosteroid drugs ransplantation of the kidney blood transfusion open heart surgery[1 1 19 9 4 7 58] should be emphasized that it also may occur in eviously healthy and unmedicated per ns[10 2 2 1 2 3 55 57]

The slightly elevated ST segments resemble the ectrocardiographic changes seen in pericarditis combined with myocarditis This interpretation is not supported by the clinical findings as our patient did not experience pericardial pain and a pericardial friction rub was never elicited



Fig 2 Chest x ray on admission showing cardiomegaly and pulmonary congestion.

The prognosis of cytomegalovirus myocarditis is not universally agreed upon Thus Sterner and colleagues[5] in two of 17 patients aged between 6 and 71 years with serologic and virologic evidence of cytomegalovirus infection and Klemola and co workers in a female patient aged 18 years and in a second female patient aged 66 years and also in a male patient aged 19 years with serolog ically verified cytomegalovirus mononucleosis saw transient flattening and inversion of T waves in the electrocardiogram Our patient with signs of heart failure distinct alterations in the electro cardiogram and cardiomegaly on x ray recov ered completely only after prolonged bedrest

In the patient of Wilson Morris and Rees there was a partial remission At the time of writing their paper the patient had survived with cardiac residuals such as alterations in electro cardiogram and cardiomegaly on x ray The 14 year old boy described by Tiula and Leinikki[7] died with signs of cardiogenic shock The main clinical manifestations were carditis hepatitis and consumption coagulopathy Myocardial in sufficiency developed and worsened in spite of digitalis treatment There was a seroconversion in

31 Klemola, E., Weckmann, N Haltia K., and Kaariainen L. The Guillain Barre Syndrome associated with acquired cytomegalovirus infection Acta Med Scand 181 603 1967

32 Klemola, E Kaariainen L., von Essen R., Haltia K. Koivuniemi, A., and von Bonsdorff C H Further studies on cytomegalovirus mononucleosis in previously healthy individuals, Acta Med. Scand. 182 311 1967

33 Klemola E., von Essen, R., Paloheimo J., and Furuhjelm, U Cytomegalovirus antibodies in donors of fresh blood to patients submitted to open heart surgery Scand J Inf Dis 1 137 1969

34 Klemola, E and Kaariainen, L Cytomegalovirus as a possible cause of a disease resembling infectious mononucleosis, Br Med. J 2 1099 1965

35 Krech, U Jung M Jung F., and Singeisen Ch. Virologische und klinische Untersuchungen bei konnatalen und postnatalen Cytomegalien Schweiz. Med Wschr 98 1459 1968

36 Kriel, L Gates G A., Wulff H., Powell N., Poland, J D and Chin T D Y Cytomegalovirus isolations associated with pregnancy wastage Am. J Obstet Gynecol 106 885 1970

37 Lamb S G and Stern H Cytomegalovirus mononucleosis with jaundice as presenting sign Lancet 2 1003 1966

38 Lang D J and Hanshaw J B Cytomegalovirus infection and the postperfusion syndrome Recognition of primary infections in four patients N Engl J Med. 280 1145 1969

39 Langenhuysen M M A C The T H Nieweg H O and Kapsenberg J G Demonstration of IgM cytomegalovirus-antibodies as an aid to early diagnosis in adults Clin. Exp Immunol 6 387 1970

40 Luthardt Th Cytomegalie Stuttgart, 1976 Ferdinand Enke Verlag.

41 Marx J L Cytomegalovirus A major cause of birth defects, Science 190 1184 1975

42 Medearis D N Cytomegalic inclusion disease Pediatr 19 46 195[illegible]

43 Mus[illegible] F K [illegible] and Rundell H Zur Rontgenuntersuchung des Herzens in horizontaler und vertikaler Korperstellung [illegible] Mitteilung Der Einfluss der Korperstellung auf das Herzvolumen Dtsch. Med. Wschr 81 1001 195[illegible]

44 Paloheimo J A von Essen R Klemola E Kaariainen, L and Siltanen, P Subclinical cytomegalovirus infections and cytomegalovirus mononucleosis after open heart surgery Am J Cardiol 22 624 1968

45 Peace R J Cytomegalic inclusion disease in adults Am J Med 24 4[illegible] 1958

46 Plotkin S A and Stetler H Treatment of congenital cytomegalic inclusion disease with antiviral agents, Antimicrob Agents Chemotherap 9 372 1969

4[illegible] Rifkind D Goodman N and Hill, R B The clinical significance of cytomegalovirus infection in renal transplant recipients Ann Intern Med 66 1116 1967

48 Rowe W P., Hartley J W., Waterman, S, [illegible] C., and Huebner R. J Cytopathogenic agent resembling human salivary gland virus recovered from tissue cultures of human adenoids Proc Soc Exp [illegible] 92 418 1956

49 Schmitz H., and Haas, R Erfahrungen mit der [illegible] zenz-serologischen Bestimmung von A[illegible] gegen Cytomegalie-Virus, Zschr Mikrobiol. Immun [illegible] 1970

50 Schmitz H., and Haas, R. Determination [illegible] cytomegalovirus immunglobulins (IgG IgM [illegible] immunfluorescence Arch. Ges. Virusforsch [illegible] 1972

51 Schmitz, H and Haas, R. Zytomegalov[illegible] bei Erwachsenen, Dtsch. Med Wschr 98 6[illegible]

52 Silk, B R., and Roome A P C H. Herpes [illegible] treated with intravenous idoxuridine Lan[illegible] 1970

53 Stern H Isolation of cytomegalovirus a[illegible] manifestations of infection at different ages B[illegible] 1 665 1968.

54 Stern H and Elek, S D The incidence of [illegible] cytomegalovirus in a normal population, J Hyg 63 79 1965

55 Sterner G Agell, B O Wahren, B and Esp[illegible] Acquired cytomegalovirus infection in older chil[illegible] adults Scand. J Infect. Dis. 2 97 1970

56 Stevens D P., Barker L F., Ketcham A S and [illegible] H. M. Asymptomatic cytomegalovirus infection [illegible] ing blood transfusion in tumor surgery J[illegible] 211 1341 1970

57 Tiula E., and Leinikki, P Fatal cytomegalovir[illegible] tion in a previously healthy boy with myocardi[illegible] consumption coagulopathy as presenting signs S[illegible] Infect Dis 4 57 1972

58 Toghill P J Bailey M E Williams, R., Zeegen [illegible] Bown, R. Cytomegalovirus hepatitis in the a[illegible] cet 2 1351 1967

59 Wahren B Espmark A., and Wallden, G Se[illegible] studies on cytomegalovirus infection in relation to [illegible] tious mononucleosis and similar conditions Sc[illegible] Infect. Dis. 1 145 1969

60 Weller Th., and Hanshaw J B Virological and c[illegible] observations on cytomegalic inclusion disease N E[illegible] Med 266 1233 1962.

61 Weller Th The cytomegaloviruses ubiquitous a[illegible] with protean clinical manifestations N Engl J [illegible] 285 203 and 285 274 1971.

62. Wilson, R S E., Morris, T H., and Rees, J R C[illegible] megalovirus myocarditis, Br Heart J 34 86[illegible] 197[illegible]

63 Zuelzer W W., Mastrangelo R. Stulberg C S P[illegible] M D Page R H., and Thompson, R I A[illegible] hemolytic anemia. Natural history and viral [illegible] logic interactions in childhood. Am. J [illegible] 1970



Fig 4 Chest x ray on discharge (see text)

nowed a high IgM antibody titer for cytomegalovirus infection of 1 1 024 and a rise of the titer or complement fixing antibody from 1 < 16 to 256 CMV could be isolated from the urine investigations for other etiological factors were negative and we assumed a connection between the cytomegalovirus infection and the myocardial involvement

We would like to thank Mr G Morrice M D Linkton Memorial Hospital Newark Ohio 430.. U S A for his assistance in the preparation of this paper

EFERENCES

Andersen H K and Spencer E S Cytomegalovirus infection among renal allograft recipients Acta Med Scand 186 7 1969

Bellamy J Cytomegalic inclusion body disease occurring in twins Am J Clin Pathol 24 1040 1954

Birdsong MacL. Smith D E Mitchell F M and Corey J M Generalized cytomegalic inclusion disease in newborn infants 162 1305 1956

Buckley T F MacCallum F O Herpes simplex virus encephalitis treated with idoxuridine Br Med J 2 419 196

Buttn k D D and Roberts, L Generalized cytomegalic inclusion disease Am J Dis Child 110 319 1965

Cangir A Sullivan M P Sutow W W and Taylor G Cytomegalovirus syndrome in children with acute leukemia J.A M A 201 118 1967

Carlstrom G Alden J Belfrage S Hedenstrom G Holmberg L, Nordbring F and Sterner G Acquired cytomegalovirus infection Br Med J 2 5?1 1968

Clavadetscher P Sulser H Linder E and Deyle P Zytomegalie Ulkus im Coecum nach Nierentransplantation Dtsch Med Wschr 99 19 0 19/4

9 Couchie A F Barton B W and Tobin O H Congenital cytomegalovirus infection treated with idoxuridine Br Med J 4 16? 1968

10 Coombs, R R H Cytomegalic inclusion body disease associated with acquired autoimmune haemolytic anaemia Br Med J 2 743 1968

11 Craighead J E Hanshaw J B and Carpenter C B Cytomegalovirus infection after renal allotransplantation J.A M A 120 725 1967

12 Diosi P Babusceac L Nevinglovschi O and KunStoi cu G Cytomegalovirus infection associated with pregnancy Lancet 2 1063 1967

13 Diosi P and David C Cytomegalic inclusion disease A historical outline Clio Medica 3 1968

14 Elek S D and Stern H Development of a vaccine against mental retardation caused by cytomegalovirus infection in utero Lancet 1 1 1974

15 Embil J A Ozere R L and Haldane E V Congenital cytomegalovirus infection in two siblings from consecutive pregnancies J Pediatr 77 417 19 0

16 Embil J A Folkins D F Haldane E V and van Rooyen C E Cytomegalovirus infection following extracorporal circulation in children Lancet 2 1151 1968

17 Fine R N Grushking C M Anand S Lieberman E and Wright H T Cytomegalovirus in children Postrenal transplantation Am J Dis Child 120 197 1970

18 Fisher E R and Davis E Cytomegalic inclusion disease in the adult N Engl J Med 258 1036 1958

19 Foster K M and Jack J A prospective study of the role of cytomegalovirus in post transfusion mononucleosis N Engl J Med 280 1311 1969

20 Hanshaw J B Steinfeld H J and White Ch. J Fluorescent antibody test for cytomegalovirus macroglobulin N Engl J Med 279 566 1968

21 Hanshaw J B and Weller H Urinary excretion of cytomegalovirus by children with generalized neoplastic disease J Pediatr 58 305 1961

22 Hanshaw J B Betts R F Simon G and Boynton R C Acquired cytomegalovirus infection Association with hepatomegaly and abnormal liver function tests N Engl J Med 272 60? 1965

23 Hanshaw J B Congenital cytomegalovirus infection laboratory methods of detection J Pediatr 75 1179 1969

24 Hem N Heissmeyer H H Schmitz H Wernet H Woenkhaus J W and Gerok W Die Cytomegalie Hepatitis im Erwachsenenalter Verhd Dtsch Ges Inn Med. 82 451 1976

25 Hem N Beck U Enders G and Schmitz G Polyneuroradikulitis Guillain Barree und Fisher Syndrom bei akuter Cytomegalie Infektion Arch Psychiat Nervenkr 222 305 1976

26 Hem N Heissmeyer H H., and Schmitz H Klinik und Diagnostik der Zytomegalie Hepatitis Dtsch Med Wschr 101 1610 1976

27 Hem N Heissmeyer H H and Schmitz H Zytomegalo virus Infektionen bei Erwachsenen Acta Med Austriaca 4 97 1977

28 Hem H Glogner P., and Schmitz H Klinik und Diagnostik der akuten Cytomegalie Infektion bei primar gesunden Erwachsenen Klin Wschr 54 1117 1976

29 Juel-Jensen B E Severe generalized primary herpes treated with cytarabine Br Med J 2 154 19 0

30 Kaanamen L Klemola E and Paloheimo J Rise of cytomegalovirus antibodies in an infectious mononsis like syndrome after transfusion Br Med J 1966

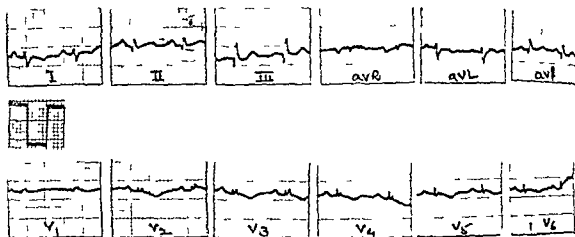


Fig 2 Electrocardiogram of the same patient as in *Fig 1* showing frontal plane QRS axis of +120 degrees, generalized low voltage QRS complexes with non specific ST T wave changes

Table I Hemodynamic data

Chamber	*Pressure*	*Oxygen saturation*
Right atrium	a = 12	
	v = 12 (10)	
Right ventricle	12/7 5 10	
Pulmonary artery	12/7 (10)	52%
Left ventricle	85/0 7	
Aorta	85/65 (72)	100%

Pressure tracing identical (see Fig 3)

Neck veins were not prominent There was no appreciable precordial impulse The heart sounds were muffled in intensity and there were no murmurs or gallop sounds Lungs were clear to auscultation A chest roentgenogram (Fig 1) showed considerable cardiomegaly the cardiac silhouette occupying almost the whole of the hemithorax Pulmonary vascular markings were unremarkable The electrocardiogram (Fig 2) revealed normal P waves a QRS frontal plane axis of +120 degrees, generalized low voltage complexes with non specific ST T changes a precordial tracing showed qr complex of very low amplitude in Lead V and very tiny complexes from Leads V to V Cardiac catheterization revealed the characteristic finding of identical right atrial right ventricular and pulmonary artery pressure tracings (Fig 3) A simultaneous electrode catheter intracardiac tracing for diagnosis of Ebstein s disease was of no help since pressure tracings of the right atrium and right ventricle were similar The left heart study revealed normal pressures (Table I) A right atrial cineangiogram showed a normally located tricuspid valve enormous dilation of the right ventricle which formed most of the cardiac contour with very scanty trabeculae (Fig 4) Pulmonary artery filling was delayed and clearance of the dye from the right ventricl was very slow a left ventricular cineangiogram was normal

These hemodynamic and angi graphic features suggested the diagnosis of parchment right ventri le with normal tricuspid valve (Uhl s anomaly) In view of persistent refractory right heart failure and the failure to thrive the child was subjected to superior vena cava right pulmonary artery anastomosis (Glenn s operation) At surgery the right atrium was found to be hypertrophied and enlarged. The right ventricle was tremendously enlarged and very thin The child was well for 3 hours after operation when sinus bradycardia to 25/minute with intermittent juntional escape beats was noted This was accompanied by profound hypotension. Parenteral atropine was of no help Transvenous right ventricular pacing was tried from different sites but capture could not be obtained and before left ventricular epicardial pacing could be tried the child died

Postmortem examination The autopsy was limited to heart and lungs The lungs showed chronic passive hyperemia and small peripheral pulmonary emboli.

Gross examination (Fig 5) The heart was enlarged. The combined weight of heart and both lungs was 250 g The right atrium was hypertrophied and enlarged The endocardial surface showed a postmortem thrombus on the right free wall There was a patent shunt between the superior vena cava and the right pulmonary artery with a purse-string suture at the junction of the right atrium and superior vena cava The tricuspid orifice was dilated but the cusps and subvalvular apparatus were normal The right ventricle was enormously enlarged with areas of sacculation The myocardium could not be recognized in the anterior surface and outflow tract of the right ventricle Scanty myocardium with trabecular pattern could be identified in portions of the inflow tract of the right ventricle and the thickness of the wall in these areas varied from less than 1 mm to 3 mm The endocardium was considerably thickened and appeared whitened in the inflow and outflow tract The pulmonary orifice diameter was normal but at the site of the pulmonary valve there were rudimentary cusps could be identified These were very thin and delicate The pulmonary trunk and branches were normal

The left atrium left ventricle mitral and aortic valves were normal The coronary arteries and its branches were normal

Microscopy

RIGHT ATRIUM The endocardium of the atrium was

hl s anomaly with rudimentary pulmonary alve leaflets A clinical hemodynamic ngiographic and pathologic study

pendra Kaul, M D., D.M
amesh Arora M D., D.M
idha Rani, M.D
w Delhi, India

s anomaly is a rare condition characterized y partial or complete absence of the myocar um of the right ventricle and its replacement by broelastic and adipose tissue in the presence of a ormal tricuspid valve[1-13] Although the orig al description was in a heart with normal ulmonic valve pulmonary atresia pulmonary enosis and atrial septal defect have been ported in association with Uhl s anomaly

he antemortem diagnosis of this condition is ry rare and only three cases have been de ribed.[3 11] The present report is the fourth ase of Uhl s anomaly diagnosed by characteristic emodynamic and angiocardiographic features he patient died in the immediate postoperative eriod following Glenn s operation Autopsy vealed partial parchment right ventricle ormal tricuspid valve and rudimentary pulmo ary valve This association has not been ported previously

ase report

V K., a 4-year-old male child, was the product of a full term ormal delivery (birth weight, 2.5 kg) When the infant was 6 onths old his mother noticed swelling of the body besides his ilure to grow well. The child was admitted to one of the city ospitals where examination revealed facial puffiness, pitting dema, muffled heart sounds, and no cardiac murmur The ver was enlarged 5 cm. below the right costal margin. In view radiological evidence of gross cardiomegaly with clear lung lds, a pericardial tap was done but no fluid could be



Fig 1 Roentgenogram of the chest of a 4 year-old male patient with Uhl s anomaly showing enormous cardiomegaly and clear lung fields.

aspirated. The child was started on digitalis and diuretics, the edema subsided and hepatomegaly regressed, but there was no change in the cardiac size Despite regular treatment, the congestive heart failure continued to progress for 3 ½ years and the child was admitted to G.B Pant Hospital, New Delhi, in August 1977 Milestones of the child were delayed. There was no history of dyspnea cyanosis, anoxic spells, or repeated chest infections.

Physical examination revealed an ill looking child (height 96 cm., weight 10 kg.) with generalized edema. There was no central cyanosis or clubbing of the digits. Peripheral pulses were regular but of low volume Blood pressure was 90/70 mm Hg. The liver edge was 6 cm below the right costal margin

rom the Departments of Cardiology and Pathology G. B. Pant ospital, New Delhi, India.

eceived for publication Nov 22, 1978.
ccepted for publication Apr 1., 1979

eprint requests Dr U pendra Kaul, N 221 Greater Kailash I, N w elhi 110 048, India.



ig 5 Autopsy specimen of the heart with the right ventricle opened up showing the trabecular pattern in the right ventricular inflow tract and the parchment like body and outflow Note the rudimentary pulmonary valve leaflets *(arrow)*

graphic findings in this condition are similar pulse contours in the right atrium right ventricle and pulmonary artery elevated right ventricular end diastolic pressure and pulmonary artery diastolic pressure due to a prominent a wave[3] The right ventricle thus functions as a reservoir for venous blood Differentiation from Ebstein s disease is possible on angiocardiography which reveals a normally located tricuspid valve in Uhl s disease with enormous right ventricular dilatation and with absent or scanty trabeculae Pulmonary artery filling is delayed Scanty delayed filling of the left heart can be seen in the levophase of the right sided angiocardiogram[3, 1] The echocardiographic findings of diastolic pulmonary valve opening increased right ventricular dimensions delayed tricuspid closure and abnormality of the mitral valve have been reported in an isolated case report The absence of a diastolic pulmonary regurgitation murmur and the normal size of the main pulmonary artery and its branches signifies that there was no appreciable pulmonary regurgitation in the present case despite rudimentary pulmonary valve leaflets

The prognosis is these cases is very poor Gasul and colleagues have suggested superior vana cava right pulmonary artery anastamosis as a surgical remedy for this condition and have reported a case with a successful outcome

The postoperative rhythm disturbance seen in our patient seems to have arisen due to surg[illegible] trauma or edema in the region of the sin[illegible] node by the purse string suture The failure of right ventricular endocardial pacing which we encountered has also been recently experienced by Bharati and associates[1] in a case of Uhl[illegible] anomaly which presented with a complete h[illegible] block and narrow QRS complexes of recent o[illegible] The conduction system examination in the[illegible] revealed total destruction of both b[illegible] branches

Summary

An acyanotic 4 year old male child who fa[illegible] to thrive presented with signs of persistent r[illegible] heart failure and no cardiac murmurs There [illegible] radiologic evidence of gross cardiomegaly w[illegible] unremarkable lung fields Cardiac catheteriza[illegible] and cineangiographic features helped in arri[illegible] at the diagnosis of parchment right ventricle w[illegible] normal tricuspid valve (Uhl s anomaly) a r[illegible] condition seldom diagnosed during life T[illegible] patient was subjected to surgery and Gle[illegible] operation was performed following which he d[illegible] of a low output state and bradyarrhythm[illegible] Autopsy revealed partial parchment right ve[illegible] cle with rudimentary pulmonary valve leafle[illegible] combination not described previously

REFERENCES

1 Uhl, H S M A previously undescribed congen[illegible] malformation of the heart Almost total absence of the myocardium of the right ventricle Bull Johns H[illegible] Hosp 9 197 1952
2 Novak, G Szanto P B Gasul B and D[illegible] Congenital aplasia of the myocardium of the right ve[illegible] tricle Proc Inst. Med Chicago 21 334 19[illegible]
3 Arcilla R A., and Gasul B M Congenital aplasia [illegible] marked hypoplasia of the myocardium of the r[illegible] ventricle (Uhl s anomaly) Clinical, angiocardiog[illegible] and hemodynamic findings J Pediatr 58 3[illegible] 1[illegible]
4 Reeve R and MacDonald D Partial absence of the right ventricular musculature—Partial parchment he[illegible] Am J Cardiol. 14 415 1964
5 Cumming G R Bowman J M and Whytehead [illegible] Congenital aplasia of the myocardium of the right ven[illegible] tricle (Uhl s anomaly) Am Heart J 70 6[illegible] 19[illegible]
6 Perrin E V., and Mehrizi, A Isolated free wall h[illegible] sia of the right ventricle Am J Dis. Child [illegible] 1965
7 Gould L., Guttman B Carrasco J and Lyon A [illegible] Partial absence of the right ventricular muscula[illegible] congenital lesion Am J Med. 42 636, 19[illegible]
8 Kinare S G Panday S R., and Deshmukh [illegible] Congenital aplasia of the right ventricular myo[illegible] (Uhl s anomaly) Dis. Chest 55 429 19[illegible]
9 Sugiura M Hayashi, T., and Ueno K. Partial absence of the right ventricular muscle in an aged, Jap Heart J 11 582 1970

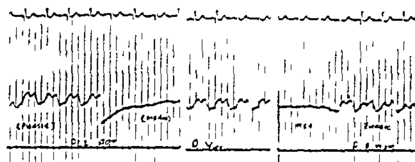


Fig 3 Pressure tracings from the pulmonary artery (PUL ART) right ventricle (RT VENT), and right atrium (RT ATRIUM) showing identical pressure pulse tracings

ne myocardium showed an increase in the elastic tissue The muscle fibers showed edema vacuolization and nuclear hypertrophy

RIGHT VENTRICLE Microsections from the anterior surface and outflow tract showed complete absence of muscle with only adipose and fibrous tissue between the endocardium and epicardium In areas of inflow where scanty muscle fibers were present, the muscle fibres showed vacuolization and degenerative changes in the cytoplasm The nuclei were bizarre in shape and there were no inflammatory cells.

PULMONARY VALVE. The pulmonary valve cusps were represented by small vestiges of fibrous tissue with only occasional areas showing endothelial lining

The left atrium, left ventricle aortic valve mitral valve aorta and pulmonary trunk were normal

Discussion

Uhl's disease is a condition with partial or complete absence of the myocardium in the right ventricle and its replacement by fibroelastic and adipose tissue in the presence of a normal tricuspid valve[1, 13] In the literature others have included parchment right ventricle with atrial septal defect pulmonic stenosis and pulmonary atresia[14] The association of Uhl's anomoly with rudimentary or absent pulmonary valve has not been reported so far The differential diagnosis of Uhl's anomaly includes conditions like Ebstein's anomaly pericardial effusion primary endocardial fiberoelastosis glycogen storage disease of the heart and anomalous origin of the left coronary artery from the pulmonary artery

The patients with this disorder present in infancy with congestive heart failure without dyspnea unless there is an associated left-sided involvement like endocardial fibroelastosis Occasionally Uhl's disease has been reported as an incidental autopsy finding

Radiological examination shows a considerable cardiomegaly even occupying the whole of the left hemithorax[2, 3] The electrocardiogram shows generalized low voltage QRS complexes with or without evidence of P pulmonale[2, 11] The great majority of cases reported in the literature were diagnosed at autopsy[11] Most of the cases described were erroneously diagnosed as Ebstein's anomaly One of the cases reported in the literature was erroneously diagnosed as mediastinal tumor necropsy established the correct diagnosis This anomaly has been diagnosed antemortem only on three previous occasions[2, 10, 5] The typical hemodynamic and angio-



Fig 4 Right atrial cineangiogram showing normally located tricuspid valve (arrow) and enormously dilated right ventricle forming most of the cardiac silhouette with absent trabecular pattern.

Dissimilar atrial rhythms A patient with triple right atrial rhythm

Luis D Suarez M.D
Andres Kretz, M D
Jose A Alvarez M.D
Jose A Martinez Martinez M D
Albino M. Perosio M D *
Buenos Aires Argentina

Partial intra atrial block seems to be a frequent electrocardiographic finding[1] Conversely dissimilar atrial rhythms due to a higher degree of intra or inter atrial block have been reported infrequently after the first clinical description[5] However since the electrical activity of one atrium or of a segment of the atria may not be registered by the conventional electrocardiogram (ECG) it seems reasonable to assume that the true incidence of these arrhythmias may have been underestimated

Recently several forms of dissimilar atrial rhythms were only detected by multiple intracardiac electrocardiographic tracings[5 11] These forms include electrical atrial standstill with flutter or tachycardia in another segment of the atria Persistent standstill of only one atrium in the absence of other heart disease has also been described[1]

We report here an unusual case of A V block and atrial fibrillation in the surface ECG in which the electrophysiological study demonstrated three areas in the right atrium each of them with different electrophysiological properties.

Case report

Clinical features A 54-year-old man followed up in the Outpatient Department because of complete A V block was referred to our laboratory for intracardiac stud[y] preceding 6 months he only complained of dizzi[ness] was no past history suggestive of heart disease a[nd] were administered. On examination he exhibited a rate of 40/minute Neither "a" waves nor can[non] were seen on the jugular veins. The blood pressure mm. Hg. A chest x ray film revealed slight cardiom[egaly] ECG showed atrial fibrillation, complete A V narrow QRS complexes, and a pattern of inco[mplete] bundle branch block. The "f" waves reflected very and could be seen only in some leads (Fig. 1A).

Electrophysiologic study After obtaining conse[nt] catheter was percutaneously introduced thro[ugh] femoral vein, and was placed across the septal le[aflet] tricuspid valve for bundle of His recordings, an[d] moved to various sites in the right atrium. Ano[ther] catheter was introduced through an antecubi[tal] pacing or recording electrograms from various right atrium, from the coronary sinus, and fro[m] ventricle An additional bipolar catheter was plac[ed] ent intraesophageal levels for recording left atr[ial] Filtered (40 to 400 Hz) intracavitary right heart e[lectrograms] were recorded simultaneously with surface leads tronics for Medicine DR 8 photographic record[er] speeds of 100 and 200 mm./sec. Electrical stimuli old, 2 msec. duration) were introduced by a Hewl[ett] Model 7804 A pacemaker

Results No atrial electrical activity could be with the catheter positioned near the sinus node 1B) and at different levels of the anterolateral right atrium. Catheter 2, placed at the highest po[rtion] interatrial septum, registered coarse fibrilloflutter interatrial septum, registered coarse fibrilloflutter is, waves of coarse atrial fibrillation (RA of Fig 1B catheter 2 was located at the lower portion of the septum and RA_1 showed the same features as However catheter 1 now placed at the coronary registered an irregular atrial activity (A waves) a 50/minute (RA) In other recording (Fig. 3), ca[theter] positioned at the atrial zone adjacent to the tr[icuspid] and fibrilloflutter waves were registered. Catheter located between both areas in which fibrilloflu[tter] ular atrial activity were obtained. The ... this tracing (RA) showed irregular waves of ver[y] tude with a rate of 450/minute These la[tter] coincide with the major deflections of RA Exc[ept]

From the Section of Cardiology Hospital de Clinicas José de San Martin," University of Buenos Aires Buenos Aires, Argentina.

Received for publication Apr 9 1 ~
Accepted for publication June 13 19~

Reprint requests Albino M Perosio M D Section of Cardiology Hospital de Clinicas Jose de San Martin A Córdoba 2351 Buenos Aires 1120, Argentina.

Associate Professor of Medicine and Chairman, Section of Cardiology University of Buenos Aires

0002-8703/80/110678 + 0 $00.50 0 © 1980 The C V

10 Zuberbuhler J R., and Blank, E Hypoplasia of right ventricular myocardium (Uhl s disease) Am J Roentgenol. Radium Ther 110 491 1969

11 Forssman O and Bjorkman G Absence of the solid part of the right ventricular musculature Acta Path. Microbiol Scand (A) 80 263 1972

12 Pérez Diaz L., Quero Jimenez, M Moreno Granados, F Pérez Martinez V., and Merino B G Congenital absence of myocardium of right ventricle Uhl s anomaly Br Heart J 35 570 1973

13 Abe T Kuribayashi R., Sato M Nieda S and Abe S Congenital hypoplasia of the right ventricular myocardium (Uhl s anomaly) A case report and review of literature J Cardiovasc Surg Torino 14 431 1973

14 Aherne W A Uhl s anomaly Arch Dis Child. 48 160 1973

15 French, J W., Baum J and Popp R L. Echocardiographic findings in Uhl s anomaly Demonstration of diastolic pulmonary valve opening Am J Cardiol 36 349 1975

16 Esposito L., and Nobili B A case of progeria associated Uhl s Syndrome Pediatria (Napoli) 83 326 1975

17 Ostermeyer J Uhl s disease partial parchment right ventricle Virchows Arch Pathol Anat 362 185 1974

18 Obma R Perry L. W and Scott L P Uhl s anomaly of the heart with atrial septal defect and valvular pulmonary stenosis, Med Ann D C 43 413 1974

19 Cote M Davignon A and Fouron J C Congenital hypoplasia of right ventricular myocardium (Uhl s anomaly) associated with pulmonary atresia Am J Cardiol 31 658 1973

20 Gasul B M Weinberg M., Luan L. L., Fell, E H Bicoff J and Steiger Z. Superior vena cava right pulmonary artery anastamosis Surgical correction for Ebstein s anamoly and for congenital hypoplastic right ventricle J.A M.A 171 1,97 1959

21 Bharati S Ciraulo D A Bilitch M Rosen K M., and Lev M Inexcitable right ventricle and bilateral bundle branch block in Uhl s disease Circulation 57 636 1978

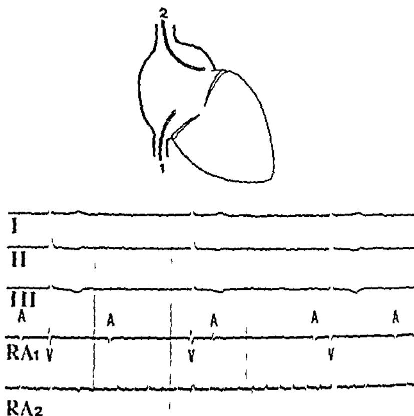


Fig 2 Catheter 1 is now placed at the coronary sinus area and its electrogram (RA) shows irregular atrial activity (A waves) with a rate of 50/minute The electrogram registered by catheter 2 positioned at the lower portion of the interatrial septum (RA) shows similar findings to those seen in *Fig 1* See text for discussion.

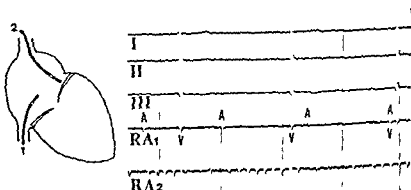


Fig 3 The fibrilloflutter waves recorded by catheter 2 located at the tricuspid area (RA) are larger than in *Fig 1* and *Fig 2* Catheter 1 is placed between areas in which fibrilloflutter waves and irregular atrial activity (A waves) are registered The isoelectric baseline of its electrogram (RA) reflects irregular fibrilloflutter waves of very low amplitude with a rate of 450 per minute These waves do not occur synchronously with the larger fibrilloflutter waves registered in RA (see text)

anterolateral wall supported by (1) no detectable atrial waves and (2) no response to atrial stimulation[11] Zone B irregular and slow atrial activity evidenced by A waves with a rate of 50/minute with apparent entrance and exit block and Zone C fibrilloflutter waves registered in the entire right surface of the interatrial septum and in the area adjacent to the tricuspid valve In Fig ... catheter positioned between Zones B ... recorded small and irregular waves pr... propagated from the latter However since ... waves occur at different times than those ... tered in Zone C and there is no regular seq... e g Wenckebach periodicity between ...

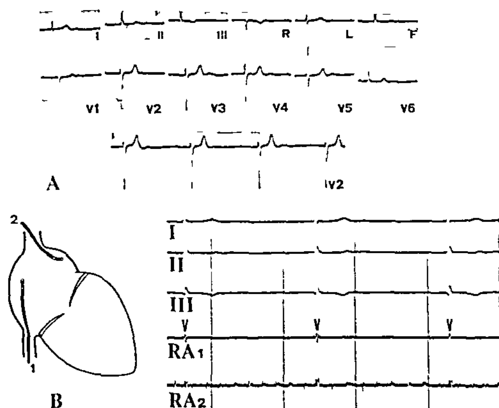


Fig 1 In this and in subsequent figures the diagram reflects the position of the catheters. RA and RA_2 are the electrograms registered with catheter 1 and catheter 2, respectively *A* Standard 12 lead ECG and rhythm strip (V) showing complete A V block with narrow QRS complexes Note the very low voltage of atrial deflections (f waves) *B* The upper electrogram (RA) reflects atrial standstill whereas the lower electrogram (RA_2) shows fibrilloflutter waves *V* = ventricular deflections. Vertical time lines are 1 sec. apart See text for details.

lation (S) with 10 to 15 mA. performed in the atrial standstill zone was not propagated, as can be seen in Fig 4*A* Catheter 1 (RA) was located 1.5 to 2 cm away from the pacing catheter (S) In Fig 4*B* the latter was positioned in the right ventricle Ventricular endocardial stimulation (S) was not conducted to the coronary sinus area registered with catheter 1 (RA) The left atrial electrograms obtained by intracoronary sinus and intraesophageal catheters reflected fibrilloflutter waves (not shown)

The electrophysiological study was repeated two weeks later and the results previously described were confirmed

In the follow up period up to 7 months the surface ECG showed similar findings, and in spite of the fact that the patient remained asymptomatic a permanent pacemaker was indicated

Discussion

The diagnostic criteria and differential diagnosis of most forms of dissimilar atrial rhythms have been well summarized by Chung As can be deduced from the analysis of these data the scalar ECG gave sufficient information about the atrial events when the sinus rhythm coexisted with other dissociated regular atrial rhythms or when flutter or fibrillation in a segment of the atria developed during sinus rhythm Conversely in the other reported forms the diagnosis was only suspected or misinterpreted

According to Wu and colleagues[8] the electrocardiographic manifestations of an atrial rhythm are dependent upon (1) the atrial mass depolarized and (2) the vicinity of the recording electrodes to this atrial mass Thus in most instances only with multiple intracavitary electrograms is it possible to demonstrate atrial events in patients with unclear forms of atrial arrhythmias

In our patient the surface ECG showed complete A V block without detectable atrial activity in most leads Only in amplified rhythm strips could a slight irregularity of the baseline be seen and the diagnosis of atrial fibrillation was established However the possibility of an atrial standstill was considered The intracardiac study demonstrated three areas in the right atrium each of them with different electrophysiological properties Zone A persistent atrial standstill in the

demonstrate atrial events in patients with atrial arrhythmias They may be of important clinical significance given the large number of new antiarrhythmic drugs with very different electrophysiological effects recently introduced On the other hand the clinical features of this and other recently reported cases[3, 4, 11] demonstrate that dissimilar atrial rhythms may be registered in several types of heart disease In contrast earlier clinical studies suggested that atrial dissociation was almost always found in critically ill patients with intractable heart failure

Summary

A patient with complete A V block and atrial fibrillation was analyzed by multiple intra atrial electrograms Three areas were recorded in the right atrium each of them with different electrophysiological properties (1) persistent atrial standstill (2) irregular atrial activity with a rate of 50/minute and (3) fibrilloflutter waves with a rate of 450/minute The latter were also registered in the left atrium

This case illustrates another form of dissimilar atrial rhythms and provides additional evidence of the importance of recording multiple electrograms from each atrium in the evaluation of the atrial events in atypical atrial arrhythmias

REFERENCES

1 Legato C L and Ferrer M Irené Intermittent intra atrial block Its diagnosis incidence and implications Chest 65 243 1974
2. Chung E K A reappraisal of atrial dissociation, Am J Cardiol. 28 111 1971
3 Perosio A. M Suárez, L D and Llera, J J Atrial dissociation Am Heart J 85 401 1973
4 Scott M E, and Finnegan, O C Atrial dissociation Br Heart J 37 539 1975
5 Schrumpf P De l interference de deux rythmes ... saux preuve du dualisme du nodule de Keith, Arch ... Coeur 13 168 1970
6 Zipes D P and DeJoseph, R. L Dissimilar ... rhythms in man and dog Am J Cardiol 32 6 ...
7 Brechenmacher C., Coumel, Ph., and Slama, R. Pa... sie auriculaire apparente et troubles de la cond... auriculo-ventriculaire Etude anatomo-clinique, ... Mal. Coeur 68 575 1975
8 Wu D Denes P Amat y Leon P Chhablani, ... and Rosen K M Limitations of the surface elect... diogram in the diagnosis of atrial arrhythmias, A... Cardiol. 36 91 1975
9 Leier C V and Schaal S F Biatrial electrogra... the diagnosis of dissimilar atrial rhythms (Abstr) C... lation 52(Suppl II) II 207 1975
10 Zipes D P., Gaum W E Genetos, B C Glassa... R., Noble R J., and Fisch, C Atrial tach... without P waves masquerading as an A V junct... tachycardia Circulation 55 253 1977
11 Leier C V., and Schaal, S F., Dissimilar atrial rh... A patient with interatrial block Br Heart J 39 ... 1977
12. Harley A. Persistent right atrial standstill, Br He... 38 646 1976
13 Waldo A L., Vitikainen K. J., Kaiser G A., Bowm... O., and Malm J R Atrial standstill secondary to ... inexcitability (atrial quiescence) Circulation 46 ... 1972
14 Cohen J., and Scherf D Complete interatrial ... intra atrial block (atrial dissociation) Am Heart ... 70 23 1965
15 Perosio A M Suárez, L D Sciandro E E, and ... J J Bloqueo interauricular Rev Argent Ca... 41 62 1973

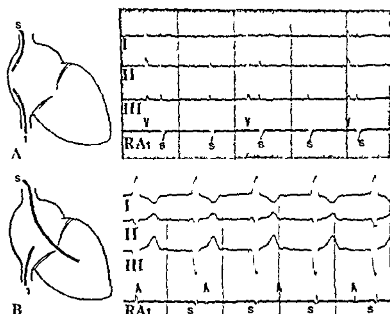


Fig 4 A Electrical stimulation performed in the atrial standstill zone (S) is not propagated (RA) Catheter 1 is located 1.5 cm away from the pacing catheter (S) B Ventricular endocardial stimulation is not conducted to the coronary sinus area recorded with catheter 1 (RA) See text

another independent atrial activity localized to a small area in the right atrium cannot be excluded In the left atrium fibrilloflutter waves were also registered His bundle electrograms were not identified in the two electrophysiological studies It is possible that the fibrilloflutter waves which were coarser in the vicinity of the tricuspid area than in the upper portion of the interatrial septum (Fig 3) masked the His potentials

Although the electrophysiological mechanism of atrial dissociation and other forms of dissimilar atrial rhythms have not yet been fully elucidated the above mentioned studies with intra atrial recordings provide evidence supporting the existence of inter and intra atrial blocks If an interatrial block is only partial a first degree of interatrial block occurs with two components (right and left) of the P waves separated by an isoelectric period as in Case 1 of Wu and colleagues[4] and in other reported cases with surface ECGs[1] If a higher interatrial block is present only some of the unilateral atrial depolarizations (right or left) are conducted to the other chamber and a second degree of interatrial block with or without Wenckebach phenomenon can be considered as in the cases reported by Zipes and DeJoseph[6] Finally if the interatrial block is complete a true atrial dissociation with two independent rhythms occurs Experimental and clinical studies suggest Bachman s bundle as the site of the block However in most cases of these so called third-degree of interatrial block the site of block appears to be located within the same atrium rather than between the two atrial chambers as in Case 2 reported by Wu and associates

In our patient the three dissimilar atrial rhythms were located in the right atrium The limits of the three different areas were well demarcated as could be demonstrated by multiple and repeated positioning of the catheters during the two electrophysiological studies performed These findings may be considered as evidence of the existence of two ectopic foci with complete exit and entrance blocks Furthermore the presence of a considerable area with atrial standstill presumably indicates an advanced degree of atrial disease This suggests that atrial fibers may show nonhomogeneous refractoriness with multiple sites of partial or complete intra atrial blocks However on the same basis it is also possible to assume the alternative explanation postulated by Zipes and DeJoseph[6] the slow atrial activity recorded in Zone B may be secondary to a constant filtering of the fibrillatory stimulus originating in Zone C and in the left atrium

The results of this study as well as previous publications emphasize the importance of recording multiple electrograms from each atrium to

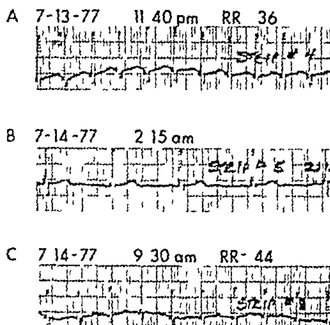


Fig 1 Holter monitor recording Patient No 1 *Panel A* was recorded during sleep and shows supraventricular tachycardia with a rate of 166 minute *Panel B* was also recorded during sleep and shows sinus rhythm *Panel C* was recorded in the early morning and shows supraventricular tachycardia at a rate of 136 minute The patient was resting quietly at the time Panel C was recorded and experienced no symptoms

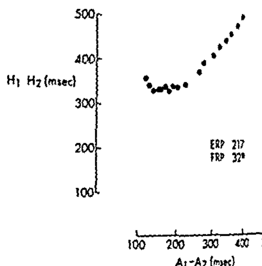
and retrograde direction was assessed by fixed rate pacing and the extrastimulus technique (Fig 2) using stimulation sites in the right atrium, coronary sinus (left atrium) and right ventricle The AV conduction system was normal and no tachycardia was induced during the study

Electroencephalographic findings The background rhythm of the EEG consisted of a well-developed and well modulated alpha rhythm at a frequency of 9 Hz The major abnormality detected was repetitive epileptiform discharges consisting of both sharp and spike wave transients arising from the lateral aspect of the right mid and anterior temporal regions These findings would provide the basis for a diagnosis of epilepsy of temporal lobe origin in symptomatic patients No cardiac arrhythmias occurred during simultaneous monitoring of the EEG and electrocardiogram

Clinical course The patient was treated initially with phenytoin 100 mg three times daily but symptoms persisted He then was treated with carbamazepine 400 mg twice a day On this dose a carbamazepine level (drawn 12 hours after the preceding dose) was 4 mcg ml After one month of therapy neurologic symptoms and all symptomatic arrhythmias had resolved A 24 hour Holter monitor recording showed only sinus rhythm

Clinical history

Patient No 2 Patient No 2 was a 15 year-old white male who was referred to Duke University in October 1976 for treatment of cardiac arrhythmia His prenatal and perinatal



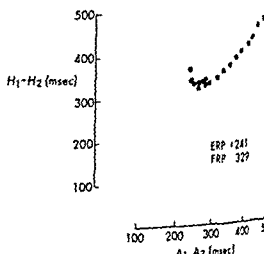


Fig 2 Refractory periods of the atrioventricular ... Patient No 1 *Panel A* right atrial pacing The ... period curve the effective refractory period, and the ... al refractory period are all normal *Panel B* ... pacing the curve is similar to the curve obtained during ... atrial pacing Atrial refractoriness prevented exact ... ment of the refractory periods of the AV node during ... sinus pacing *ERP* = effective refractory period *FRP* ... tional refractory period

history was unremarkable His mother commented that ... infant he appeared to have a rapid heart rate but ... were not recorded At age 12 he had an episode of ... consciousness He was taken to a hospital emergency ... where a diagnosis of atrial flutter was made He was ... digoxin One month later he had a second episode of ... consciousness Both bradycardia and tachycardia ...

Arrhythmogenic epilepsy an hypothesis

Edward L C Pritchett M D *
James O McNamara M D **
John J Gallagher M D ***
Durham N C

Spontaneous paroxysmal supraventricular tachycardia (PSVT) can almost always be reproduced in patients with this arrhythmia by programmed stimulation in the electrophysiology laboratory [3] The arrhythmia may be caused by reentry within the atrioventricular (AV) node reentry within the sinus node or reentry using an accessory A V pathway [3] We recently studied two patients who had multiple arrhythmias including PSVT Electrophysiologic mechanisms for the arrhythmias could not be demonstrated by programmed stimulation in either patient Both patients were found to have epileptiform abnormalities demonstrated by electroencephalogram (EEG) A primary neurologic abnormality was the probable cause for the arrhythmias in these patients

Case reports

Patient No 1

Clin cal history Patient No 1 was a 21 year old college student when he was referred to Duke University in April 1978 for treatment of cardiac arrhythmias His first recollection of symptoms suggestive of tachycardia occurred in October 1976 At that time he was bowling and experienced dizziness and dyspnea A nurse was present and stated that his pulse was very fast " The episode terminated abruptly after 30 minutes Two weeks later he experienced palpitations dyspnea, and nausea in a restaurant Observers reported that he lost consciousness for approximately 10 minutes but was not incontinent and did not have tonic or clonic seizures He awoke and returned home where his mother felt his pulse and noted that it was approximately 200 beats/minute He continued to have two or three attacks of altered consciousness per month between October 19"6 and July 19 7 Some attacks were accompanied by palpitations other similar episodes were not In July 1977 a Holter monitor recording demonstrated two episodes of supraventricular tachycardia (Fig. 1) that caused no symptoms During tachycardia the QRS morphology was normal. He was treated with digoxin, propranolol quinidine and combinations of these drugs but none modified the frequency or severity of tachycardia or dizziness. He was referred for further evaluation and treatment

The vital signs were normal and the cardiovascular and neurologic systems were normal by clinical examination An electrocardiogram recorded at the time of admission was normal

The patient had four hospital admissions between April and August 19"8 During these hospitalizations he had continuous monitoring of his electrocardiogram in the Coronary Care Unit Holter monitor recordings were also made The dominant arrhythmia was sinus arrest with an ectopic atrial pacemaker at a rate slower than the sinus rate The patient had no symptoms and no spontaneous tachycardias while in the hospital

Results of electrophysiologic testing Basic A V conduction intervals are shown in Table I Sinus node recovery times were normal. The A V conduction system in the antegrade

Table I Conduction intervals

	Patient 1	*Patient 2*
Sinus cycle msec (beats/min)	"30 (82/min)	465 (129/min)
PA interval (msec)	40	20
AH interval (msec.)	60	50
HV interval (msec)	40	45
QRS morphology	normal	normal

From the Division of Cardi logy d N urology of th Dep tm nt f Medicine, Duk U iv rsity Medical Center Durham N C

Supported in part by Grant RR-30 from th G n r l Clini al Research Ce ters Branch Di ision f H lth Resou es B thesda Md

Received f r publication Jun 14 1979

Accepted f r publicati n July 18 19 9

Send c rrespond nce to Edw rd L. C Pritchett M D Duke Unive sity Medical C nter Dept of Medicin D vis on of Cardio ascular Disease Durham N C 2"710

*Dr Pritch tt is th recip ent of NHLBI You g In estig t Resear h Aw rd HL 21347 Dr Pritch tt is Assistant Professor of Medicin Di isi n f Cardi l gy nd Asso iate Direct of th Clin cal Electro physiology Laborat ry Duk University Medi l C nt

**Assistant Pr fessor of Medicin D visi n of Neur l gy nd Direc o The Epil psy C nter Durham V t ans Administrat n Hosp al.

***This w rk was d n during Dr G llagh t nure as n Established n estig t r of th Am rican H art Assoc t n. D G llagh is Associate Professor f Medicine, D vis on of Cardi logy and Directo he Clinical Electrophy ol gy Labor tory Duke Un ersity Medical Center

00?-8 03/80/110683 + 06$00 60/0 © 1980 The C V Mosby Co

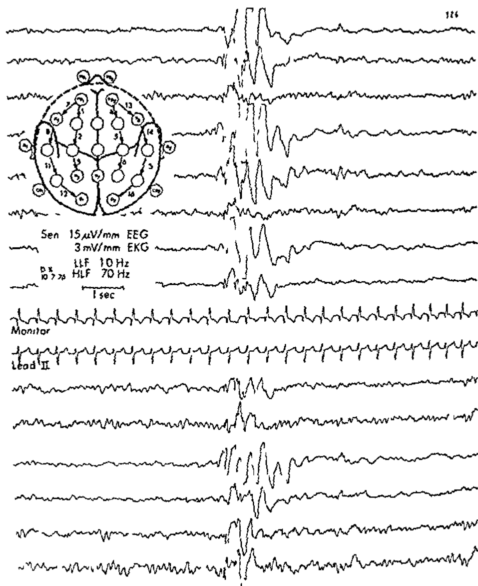


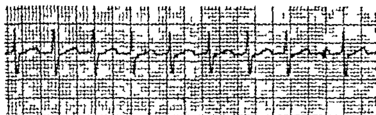
Fig 4 Epileptiform discharges on EEG on Patient No 2 Supraventricular tachycardia is present throughout the tracing

one case to drive a car) even though tachycardia persisted

Paroxysmal supraventricular tachycardia was a prominent arrhythmia recorded in both patients but three features of the arrhythmia were unusual As noted above PSVT rarely causes loss of consciousness Also common antiarrhythmic drugs failed to alter the frequency duration or severity of attacks In addition no etiology could be found for the PSVT and other arrhythmias when electrophysiologic studies were done This arrhythmia has been studied intensively with electrophysiologic techniques for several years The etiology can be demonstrated by laboratory methods in approximately 90% of patients in whom PSVT occ… spontaneously [13]

Both the presence of neurologic sympt… without arrhythmias and the unusual feat… the PSVT led us to consider alternate expl… tions in these patients referred for cardiac e… ations A primary neurologic abnormality ca… seizures and subsequent initiation of arrhyt… was an hypothesis that would explain all … findings Epileptiform discharges on the … EEG of both patients supported this … hypothesis

A correlation between the EEG abnorm… and the cardiac arrhythmias would p… important evidence implicating the epilep…



D K M32823
9-11-76 10 55 a m

Fig 3 Paroxysmal supraventricular tachycardia Patient No 2 This tachycardia had been present for over 12 hours when its termination was recorded on this monitor lead The last QRS was the result of a sinus beat

described at the time of the second attack. Phenobarbital 30 mg. orally twice daily was added to digoxin and propranolol 10 mg orally twice a day was begun in 1975 He continued to have dizzy spells, bradycardia and tachycardia He lost consciousness again in December 1975 was taken to a hospital emergency room and was found to have a rapid supraventricular tachycardia Phenobarbital was increased to 30 mg three times daily and propranolol was increased to 20 mg also three times a day Quinidine 200 mg four times daily was begun in February 1976 and digoxin and phenobarbital were continued. In September 1976 he again lost consciousness His heart rate recorded by the school nurse was 180 beats/minute He was admitted to a hospital and PSVT converting to sinus rhythm was recorded on a monitor lead (Fig 3) He was referred for further evaluation and treatment

The vital signs were normal and the cardiovascular and neurologic systems were normal by clinical examination An electrocardiogram recorded at the time of admission was normal.

During the course of hospitalization the patient was observed with continuous ECG monitoring in the Coronary Care Unit A variety of arrhythmias were documented including sinus tachycardia (rate 210 beats/minute) sinus arrest (2 6 second pauses) junctional rhythm with retrograde block junctional rhythm with retrograde conduction multifocal ventricular tachycardia, first-degree atrioventricular (A V) block, Mobitz Type I second-degree A V block and high grade A V block During periods of sinus rhythm there were frequent episodes of sinus arrest followed by appearance of an ectopic atrial pacemaker at a rate slower than the sinus rate (similar to the rhythm recorded in Patient No 1) No symptoms occurred during arrhythmias

Results of electrophysiologic testing Basic conduction intervals (Table I) and sinus node recovery times were normal Using stimulation sites in the right atrium and right ventricle electrophysiologic tests were performed The A V conduction system was tested with fixed rate pacing and the extrastimulus technique The A V conduction system was normal and no tachycardia was initiated

Electroencephalogram findings The background rhythms of the EEG consisted of a well developed alpha rhythm at a frequency of 9 Hz The principal abnormalities consisted of (1) irregular intermittent theta and delta transients in the left temporal regions throughout the waking record and (2) bilaterally synchronous 3 to 4 per second spike and wave discharges maximal in amplitude in the frontal and central regions (Fig 4) Despite the focal theta and delta transients in the left temporal region no focal (as opposed to bilaterally synchronous) cortical spiking was detected The focal slowing suggested the presence of a structural lesion in the left temporal region. The synchronous spike wave discharges would be consistent with a diagnosis of cortical reticular epilepsy in a symptomatic patient Supraventricular tachycardia was detected by simultaneous monitoring of the electrocardiogram during the EEG However the supraventricular tachycardia did not reflect a consistent temporal relation to occurrence of EEG abnormalities

Clinical course A ventricular demand pacemaker was implanted in October 1976 He began taking phenytoin 100 mg three times a day He continued to have supraventricular tachycardia Treatment with digoxin 0.25 mg three times daily was begun Supraventricular arrhythmias persisted and digoxin was discontinued and propranolol and a combination of propranolol and disopyramide were tried. No combination of drugs prevented tachycardia but the patient did not have another episode of loss of consciousness The patient was found dead in a swimming pool in April, 1978 At the time of death, the pacemaker was functioning normally The brain was normal at autopsy

Discussion

The ages of these patients and several other factors strongly suggest that the arrhythmias in these two patients did not cause the neurologic symptoms Paroxysmal supraventricular tachycardia is not usually associated with syncope in children and one patient had episodes of dizziness and disorientation which were not accompanied by palpitations Also during episodes of loss of consciousness accompanied by tachycardia the tachycardia persisted after consciousness returned Neurologic symptoms secondary to an arrhythmia usually last as long as the arrhythmia does or until the victim has fallen to a recumbent position When consciousness returned our patients were able to resume normal activities (in

10 Lown B and Verrier R L. Neural activity and ventricular fibrillation N Engl J Med 294 1165 1976
11 Fuster J M, and Weinberg S J Bioelectrical changes of the heart cycle induced by stimulation of diencephalic regions Exper Neurol 2 26 1960
12 Walsh, G O Masland W, and Goldensohn E S Relationship between paroxysmal atrial tachycardia and paroxysmal cerebral discharges Bull Los Angeles Neurol Soc 31 28 1972
13 Steiner C, Wit A L, Weiss, M B and Damato A N The antiarrhythmic actions of carbamazepine J Pharmacol Exp Ther 173 323 1970
14 Livingston S Pauli, L L, and Berman W Carbamazepine (Tegretol) in epilepsy Dis Nerv Syst 35 103 1974
15 Phizackerley P Poole E and Whitly C Sinoauricular heart block as an epileptic manifestation, Epilepsia 1· 1954
16 Poggiali, I Considerazioni su di un caso di ta... parossistica con alterazioni electroencefalografiche C... ca Pediatrica 53 760 19 1
17 Lown B DeSilva R A and Lenson, R. P... psychologic stress and autonomic nervous sys... changes in provocation of ventricular prema... plexes Am J Cardiol 41 979 1978
18 Lown B Temte J V, Reich, P Gaughan, C, F... stein, Q and Hai, H. Basis for recurring ve... fibrillation in the absence of coronary heart disease... its management, N Engl J Med 294 623, 197...
19 Wellens H J J Vermeulen A and Durrer D Ven... ular fibrillation occurring on arousal from sle... auditory stimuli, Circulation 46 661 1972.

IMPORTANT
INFORMATION FOR AUTHORS

All manuscripts for the AMERICAN HEART JOURNAL should be sent to

Dean T Mason M D
Section of Cardiovascular Medicine
University of California
School of Medicine
Davis California 95616

discharges as a cause for the cardiac arrhythmias Despite the occurrence of the cardiac arrhythmia during EEG monitoring in Patient No 2 such a correlation was not established This finding is not surprising in light of two facts First even when abnormally excitable neural tissue lies in immediate proximity to the scalp (e g *epilepsia partialis continuans* arising from precentral gyrus) a close correlation between epileptiform discharges on EEG and the clinical seizure can be established in less than 50% of cases Second accurate sampling of epileptiform activity in depths of the brain by sampling scalp EEG is exceedingly difficult Since the brain regions implicated by stimulation studies as causing arrhythmias are remote from the scalp (e g diencephalon and orbital frontal cortex) [1] difficulties in establishing a close correlation would be expected Thus the failure to establish a one to one relationship between the PSVT and the scalp EEG abnormalities in no way excludes seizures as a cause of the arrhythmias

Walsh and colleagues[1] described a patient in whom a supraventricular arrhythmia occurred immediately following the onset of epileptiform discharges on the EEG Unfortunately electrophysiologic testing of that patient was not done and the absence of an intrinsic cardiac abnormality can not be assumed

Abolition of both the arrhythmia and the neurologic symptoms in Patient No 1 by a single antiepileptic agent carbamazepine is consistent with the primary neurologic cause of a cardiac arrhythmia postulated Carbamazepine has some antiarrhythmic effects on ventricular tachycardia induced by digitalis or coronary artery ligation in dogs[1] It is however also related to the tricyclic antidepressants that have arrhythmogenic potential in man The effect of carbamazepine on arrhythmias in humans is not known

The findings in our two patients in which arrhythmias appeared to be secondary to partial seizures strengthen the argument that some arrhythmias have a nerual origin Arrhythmias have been induced by stimulation of the diencephalon of experimental animals and bradycardia[1] and tachycardia have been reported in humans with epilepsy Recent investigation of the neural influence on arrhythmias has identified an important role for psychologic stress Potentially lethal arrhythmias have been linked to psychologic stress in two patients who had no known cardiac abnormalities [19] Future study of the origin of arrhythmias may include studies of the neurologic system

Summary

This report describes a clinical syndrome of arrhythmias that may have neural origin Two patients presented with episodes of loss of consciousness disorientation and paroxysmal supraventricular tachycardia (PSVT) One patient reported experiencing neurologic symptoms without tachycardia When electrophysiologic testing with intracardiac recordings and programmed stimulation yielded no abnormalities that could account for the arrhythmias a primary neurologic abnormality was sought The electroencephalograms of both patients showed epileptiform discharges that supported this hypothesis Arrhythmias and neurologic symptoms were controlled by treatment with the antiepileptic drug carbamazepine in one patient Findings in these two patients suggest that in some patients arrhythmias may be a manifestation of seizures

REFERENCES

1 Goldreyer B N and Bigger J T Site of reentry in paroxysmal supraventricular tachycardia in man, Circulation 43 15 1971
2 Denes P Wu D Dhingra R C Amat y Leon, F., Wyndham C R C and Rosen K M Dual AV nodal pathways Br Heart J 37 1069 1975
3 Wu D Denes P Amat y Leon F Dhingra R Wyndham C R C Bauernfeind R Latif P and Rosen K M Clinical electrocardiographic and electrophysiologic observations in patients with paroxysmal supraventricular tachycardia Am J Cardiol 41 1045 1978
4 Pritchett E L C Gallagher J J Sealy W C Anderson R Campbell R W F., Sellers T D Jr and Wallace A G Supraventricular tachycardia dependent upon secondary pathways in the absence of ventricular preexcitation Am J Med 64 214 1978
5 Benditt D G Strauss H C Scheinman M M Behar V S and Wallace A G Analysis of secondary pauses following termination of rapid atrial pacing in man Circulation 54 436 1976
6 Wit A L Weiss M B Berkowitz W D Rosen K M Steiner C and Damato A N Patterns of atrioventricular conduction in the human heart Circulation 27 345 1979
7 Nadas A S Daeschner C W Roth, A and Blumenthal S L Paroxysmal tachycardia in infants and children Pediatrics 9 167 1952
8 Saunders E D and Ord J W The hemodynamic effects of paroxysmal supraventricular tachycardia in patients with the Wolff Parkinson White syndrome Am J Cardiol. 9 223 1962
9 Thomas J E Reagan T J., and Klass D W Epilepsia partialis continua A review of 32 cases Arch Neurol. 34 266 1977

Table I Microbiology of infective endocarditis

	Patients			
	1951 through 1957		1972 through 1976	
	No	%	No	%
Viridans streptococci	91	53	81	37
Group D streptococci	28	16	36	17
Staphylococcus aureus	24	14	33	15
Staphylococcus epidermidis	4	2	13	6
Gram negative bacilli	10	6	24	11
Other microorganism	1	1	25	11
Negative blood cultures	14	8	7	3
Total	172	100	219	100

Including fungi. (From Wilson W R and Washington J A II Infective endocarditis—a changing spectrum? (Editorial) Mayo Clin Proc 52 2.4 1977 Reproduced by permission.)

1970s however the average number of cases of IE increased from 24 5 per year 20 years ago to 44 per year during the 1970s and the number of patients with viridans streptococcal infections increased from [illegible] per year It is clear that there are [illegible] patients with viridans streptococcal IE [illegible] more patients with IE caused by [illegible] microorganisms Part of this changing spectrum [illegible] the result of nosocomially acquired infection associated with the increased use of intravascular prostheses life support mechanism monitoring systems and invasive diagnostic techniques Another factor in the changing microbiologic spectrum of IE is the apparent increase in the number of patients with IE associated with intravenous drug abuse Nosocomially acquired IE or IE associated with intravenous drug abuse is often due to gram negative bacilli *Candida* and opportunistic microorganisms—uncommon causes of IE in the 1950s

Despite the changing spectrum of IE at least 75% of infections are caused by streptococci or staphylococci The selection of antimicrobial agents for the therapy of infections caused by these microorganisms depends on the penicillin susceptibility of these isolates An understanding of the differences between streptococci and staphylococci that are susceptible to penicillin and those that are resistant to penicillin is essential for the selection of appropriate antimicrobial agents and frequently for determining the length of antimicrobial therapy

Role of blood cultures in diagnosis of IE

In patients with suspected IE the most imp[illegible] tant laboratory finding is the isolation of bacteri[illegible] or fungi from at least two or more blood cult[illegible] obtained at intervals during a 48 hour per[illegible] Bacteremias associated with IE are usu[illegible] continuous[6,7] and if any blood cultures are p[illegible] tive, most of the other cultures drawn will al[illegible] positive[8,9] Although bacteremia is prob[illegible] continuous Weiss and Ottenberg[1] found s[illegible] showers of larger numbers of bacteria tempor[illegible] related to an increase in patients body temper[illegible] tures Wright[11] was unable to document [illegible] temporal association with fever The ord[illegible] magnitude of bacteremia is usually relatively [illegible] In 83% of cases the quantitative blood cul[illegible] contained less than 100 colonies per mi[illegible] ter[7,9,10] Studies have shown that cultures [illegible] peripheral venous blood are as likely to be p[illegible] tive as those of arterial blood[7,8,1] Blood cul[illegible] should not be obtained through a preexis[illegible] intravenous catheter because pericatheter c[illegible] taminants or colonizers may be drawn up in [illegible] blood sample and contaminate the blood cul[illegible] medium[12]

Belli and Waisbren[11] reported that 5? of [illegible] cases of IE were diagnosed with the first bl[illegible] culture and in only six cases were more than [illegible] blood cultures necessary Werner and associ[illegible] in a similar study, found that streptococci [illegible] isolated in 96% of cases from the first b[illegible] culture and in 98% from one of the first two b[illegible] cultures Staphylococci were isolated from [illegible] first culture in 90% and from one of the fir[illegible] cultures in 100% of cases Antimicrobial the[illegible] given within 2 weeks before blood cultures [illegible] obtained reduced the positive cultures in [illegible] cases of streptococcal endocarditis from 9? to [illegible] ($P < 0.02$)[9] In cases of IE caused by microor[illegible] isms other than streptococci and staphylococ[illegible] the causative agent was isolated from 82% of c[illegible] in the first blood culture and from 100% in ca[illegible] the first two blood cultures[9]

In conclusion on the basis of the above d[illegible] patients who have not received prior antim[illegible] bial therapy, it is rarely necessary to ob[illegible] than three separate sets of blood cultures [illegible] 24 hour period on two consecutive days [illegible] patients suspected of having IE The t[illegible] collection of blood cultures just before an [illegible] pated increase in temperature may [illegible] increase the likelihood of a positive blood cu[illegible]

Infective endocarditis therapeutic considerations

Walter R Wilson M D
Donald R Nichols M D
Rodney L Thompson M D
Emilio R Giuliani M D
Joseph E Geraci M D
Rochester Minn

During the preantibiotic era recovery from serious bacterial infections was not uncommon That patients survived these infections is testimony to the major role played by host defense mechanisms in controlling or eradicating many types of bacterial infections This is not the case with infective endocarditis (IE) Host defense mechanisms play little role in the control of IE and before the discovery of antibiotics the mortality rate of patients with IE was virtually 100% In no other infection does cure seem to be so dependent upon the administration of appropriate bactericidal antimicrobials The pathophysiologic events that result in the formation of valvular vegetations composed of dense networks of avascular fibrin platelet matrices appear to protect microorganisms buried within from phagocytes and other host defense mechanisms

Effective antimicrobial therapy exists for most patients with IE The role of the microbiology laboratory in the selection of appropriate antimicrobial therapy is probably more important in the management of patients with IE than in that of any other infectious disease process The purpose of this paper is to discuss the microbiologic spectrum of IE the role of the microbiology laboratory and the rationale for the selection of antimicrobial therapeutic regimens and to consider general principles for the medical and surgical management of patients with IE

[1] From the Mayo Clinic and M y Fo ndation Rocheste Minn.
Recei ed for publication March 6, 1979
Reprint requests Walter R. Wilso M.D Department of Internal Medicine Mayo Clinic and Mayo Foundati n, Rochester Minn. 55901

Microbiologic cause of IE

Virtually any microorganism is capable of causing IE[1] Table I lists the microbiologic causes of IE in 172 patients seen at the Mayo Clinic from 1951 through 1957 and compares these data with those from 219 patients with IE treated at the Mayo Clinic 20 years later The data presented in Table I suggest that the microbiologic causes of IE in the 1950 s differed from those of the 1970 s The increasing number of reports describing uncommon causes of IE is probably attributable to two factors (1) improved microbiologic techniques and (2) a changing microbiologic spectrum The impact of improved microbiologic techniques is apparent in patients with gram negative bacillary other infections and culture negative endocarditis Some gram negative bacilli such as *Haemophilus* species are slow growing microorganisms with special growth requirements These fastidious microorganisms constitute a major portion of the gram negative bacillary cases of IE in the later group of patients seen at the Mayo Clinic Of the 25 patients seen with IE in the 1970 s caused by other microorganisms six had infections with anerobic gram positive cocci In the 1950 s anerobic microbiology was largely a research tool and patients with IE due to anerobic bacteria would have been classified as culture negative Although improved techniques may explain some of the differences between IE of the 1950 s and that of the 1970 s the experience at the Mayo Clinic and elsewhere indicates that the bacterial spectrum of IE is changing The percentage of patients with viridans streptococcal IE seen at the Mayo Clinic declined from 53% in the 1950 s to 37%

0002-8 03/80/110689 + 16$01 60/0 © 1980 The C V Mosby Co.

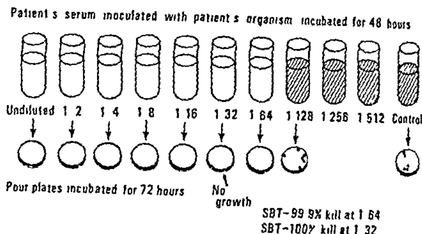


Fig 2 In vitro susceptibility testing serum bacterial test

cin) the serum sample should be obtained at the anticipated peak concentration of the agent administered intermittently A standard inoculum of the patient s bacteria is transferred to each tube and the tubes are incubated at 37° C for 48 hours Tubes showing no visible evidence of growth and the last tube showing growth are subcultured into pour plates as described above The results are expressed as the highest dilution of patient serum which kills 99 9 to 100% of the inoculum Although it is difficult to interpret accurately the results of the SBT considerable clinical experience suggests that antibiotic treatment should be adjusted to achieve a peak serum concentration of antimicrobials which results in an SBT of 1 8 or more

It is desirable to measure serum concentrations of antibiotics from the same specimen of serum used to determine SBT The serum concentrations assist in the interpretation of the SBT A low SBT may be related to a simultaneously low serum concentration of antimicrobial rather than to a lack of bactericidal effect and this suggests that the dosage should be increased Serum concentrations should also be measured periodically throughout the course of treatment to ensure adequate therapeutic levels in excess of the MBC and to avoid accumulation in the serum of potentially toxic concentrations of antimicrobials

Occasionally with unusual organisms or those resistant to multiple drugs or as a guide for determining optimal combinations of antimicrobials in vitro tests of synergism between antimicrobials may be desirable Methods for determining antimicrobial synergy have been described [23-25]

Treatment of IE—general considerations

A number of general principles sho[...] adhered to in the treatment of all patient[...] IE

1 It is important to establish the microbi[...] diagnosis if possible before starting anti[...]bial therapy In the subacute form of IE, pa[...] often have been ill for weeks or months, a[...] is usually no great urgency to initiate anti[...]bial therapy Failure to establish the mi[...]logic cause in cases of suspected IE may re[...] prolonged hospitalization with increased c[...] the patient multiple iatrogenic complica[...] related to the use of inappropriate therapy[...] possible relapse of the infection In contra[...] patients with acute septic IE the use of an[...]crobials should not be delayed until the re[...] blood cultures or other laboratory studie[...] known Therapy should be begun promptl[...] blood has been obtained for the initial set of b[...] cultures The importance of the use of bacter[...]al antimicrobials and SBT determinat[...] emphasized above

2 In urgent cases in which empiric antimi[...]bial therapy must be initiated before the c[...]tive agent has been identified the regimen s[...] include a combination of antibiotics e[...] against enterococci and penicillinase-prod[...] staphylococci

3 It is preferable to treat patients with I[...] facilities where emergency cardiac valve rep[...]ment may be performed if necessary Pa[...] with aortic valve IE may experience acute a[...] insufficiency with severe congestive heart fa[...] Immediate cardiac valve replacement in [...] patients may offer the only hope of survival[...]

4 In general antimicrobial therapy sho[...]

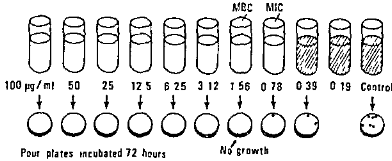


Fig 1 In vitro susceptibility testing minimum bacterial concentration

but the limitations of this recommendation are obvious An important exception to the reports that state that blood cultures are usually positive in patients with IE is that of patients with fungal IE Patients with IE caused by *Candida* species often have positive blood cultures however other causes of fungal IE notably *Aspergillus* species are usually associated with negative blood cultures Diagnosis may occasionally be established by staining and culturing emboli removed surgically from peripheral vessels [1] More often the diagnosis of fungal IE is made at the time of cardiac valve replacement or at autopsy

In vitro susceptibility testing

It is important to determine accurately the in vitro susceptibility of organisms causing IE The most widely used test and the simplest to perform is the minimum inhibitory concentration (MIC)—the lowest concentration of antibiotic which will inhibit the growth of the causative bacteria MIC may be measured by disk diffusion agar dilution or broth dilution methods

The minimum bactericidal concentration (MBC)—the lowest concentration of antimicrobial which will kill 99 9 to 100% of the inoculum—is also helpful in determining optimal therapy The broth dilution technique is used to determine MBC (Fig 1) Briefly described 10 serial twofold dilutions of the desired antibiotic are prepared in nutrient broth in sterile test tubes The concentration of antibiotic in the 10 tubes of nutrient broth decreases sequentially—100 µg/ml in tube 1 50 µg/ml in tube 2 25 µg/ml in tube 3 and so on to 0 19 µg/ml in tube 10 A standard inoculum of the patient s bacteria is then added to each tube After overnight incubation at 37° C the tubes are examined The lowest concentration of antibiotic which completely inhibits visible growth as indicated by lack of turbidity in the media is the MIC From each of the tubes that have no visible turbidity and from the first tube exhibiting the turbidity aliquots are removed and subcultured into media for pour plates After 48 and 72 hours of incubation the lowest concentration of antibiotic which kills 99 9% of the inoculum (less than 10 colonies per plate) or 100% of the inoculum is recorded as the MBC

The disk diffusion or agar-dilution MIC provides valuable information for the *initiation* of antimicrobial therapy However most clinicians experienced in the treatment of patients with IE believe that broth-dilution MIC and MBC are more accurate in indicating susceptibility The concentration of antimicrobial agents achieved in fibrin clot vegetations may be less than that measured in serum and dosages of antimicrobials should be adjusted so that ideally the peak serum concentration of antimicrobial exceeds the MBC

The serum bactericidal test (SBT) is a modification of the broth dilution test of antimicrobial susceptibility Instead of serial dilutions of an antimicrobial solution serial twofold dilutions are prepared of the patient s serum containing the antibiotic that has previously been administered to the patient (Fig 2) Serum samples should be obtained at the anticipated peak serum antimicrobial concentration usually 1 hour after administration of an antibiotic If the patient is receiving two antimicrobials one continuously and one intermittently (that is continous intravenous penicillin and intramuscular streptomy

tive therapy outlined below or presented in standard texts and references

Penicillin sensitive viridans and nonenterococcal group D streptococcal IE (MIC $\leqq$ 0 1 $\mu g/ml$)

Penicillin sensitive viridans and nonenterococcal group D streptococci are the most frequent causes of IE, constituting at least 45% of all cases [1 4] These organisms are part of the normal microbial flora of the oral cavity and gastrointestinal tract Species of viridans streptococci are especially common in the oral cavity where they form plaques on the surface of teeth At least one species *Streptococcus mutans* is important in the production of dental caries [27] It has been recognized for many years that dental manipulations may result in transient polymicrobial bacteremia, and a history of recent dental procedures often antedates the onset of symptoms of IE [3 28 31] Viridans streptococci are considered noninvasive saprophytes and why these rather placid organisms and not other more aggressive microbes found in the oral cavity, result in IE has been a subject of considerable interest Recent studies have demonstrated that viridans streptococci *S bovis* and some enterococci are considerably more adherent to the endothelium of heart valves than are other bacteria This increased adherence is probably due to the production of dextran which increases bacterial stickiness [33 35] Not coincidentally then viridans and nonenterococcal streptococcal IE is most often caused by dextran producing strains—*S sanguis S mutans S bovis*—and IE caused by non dextran producing strains—*S salivarius*—is rare [3 39]

Hunter originally suggested the use of combined penicillin streptomycin therapy for treatment of viridans streptococcal IE based on in vitro studies demonstrating synergy against isolates of viridans streptococci [4] That the combination of penicillin and streptomycin is superior to penicillin alone in the treatment of these infections is supported by data collected from studies of experimental animal IE Combined penicillin and streptomycin was more effective than penicillin alone in preventing experimental endocarditis and in the treatment of established infection In patients with IE caused by viridans streptococci who were treated with dihydrostreptomycin and low dose penicillin therapy [46] early studies reported relapse rates of 6 to 11%

Table II lists three generally accepted meth and alternatives for the antimicrobial thera penicillin sensitive viridans and nonenteroco group D streptococcal IE Recently reported [1 49] a prospective study of 68 patie with streptococcal IE (54 patients with vi and 14 with *S bovis* infections) who were tre with short term combined intramuscular thera with procaine penicillin and streptomyc i none of these patients did the infection re and the mortality rate was 3% Earlier o e (J E G) reported only one relapse amon surviving patients treated for 2 weeks with va ing dosages of intramuscular penicillin and str tomycin [49 51] Together with our 68 patients th additional 66 patients constitute a total of 1 patients who were treated similarly with o one relapse (0 7%) Some authors suggest patients whose symptoms have been pres f more than 3 months may be at higher ri relapse and that treatment should be conti with penicillin G alone for an additional 2 weeks However 14 of our 68 patients (21%) who w treated with short term therapy had sym for more than 3 months and in none was th relapse Moreover two of our 68 patients ha a relapse elsewhere after 4 weeks of intrave penicillin G therapy alone and both pati were cured with short term combined therap

Some viridans streptococci are relatively re tant to penicillin (MIC > 0 1 $\mu g/ml$ MBC $\geqq$ 3 12 $\mu g/ml$) Some investigators that patients with infections caused by th relatively penicillin resistant microorga should receive antimicrobial therapy identic that for enterococcal endocarditis (see b and Table III) In our study 37% of isolate relatively penicillin resistant according to criteria [31] All of these patients were cur infection with 2 weeks of intramuscular com penicillin streptomycin therapy

Wolfe and Johnson [3] found no relapses i retrospective study of 35 patients with IE c by penicillin sensitive viridans streptococ were treated with a mean daily dose of 1 million units of penicillin for 30 4 days and 1 of streptomycin for 13 4 days In unpu data these authors cite in excess of 60 add patients treated similarly without relapse T sett and Hurst [1] reported no relapses in 60 patients in whom a similar therapeutic men had been used

Streptomycin associated vestibular t

. red parenterally rather than orally ... otion from the gastrointestinal tract of orally administered antimicrobial agents may be unpredictable

5 Patients who are receiving treatment for IE should be examined daily throughout their hospital course Subtle changes in body weight blood pressure cardiac auscultatory findings jugular venous distention and so on may presage abrupt hemodynamic decompensation Clinicians should also be alert for the occurrence of large arterial ... especially in patients with IE caused by *Haemophilus* species or by fungi

6 Within 48 hours after initiation of specific ...crobial therapy, blood cultures should be ...ined to assess the efficacy of treatment Persistently positive blood cultures in spite of apparently appropriate treatment could indicate myocardial aortic root or distant abscesses tolerance of bacteria to antimicrobial agents or error in administration or dosage of antimicrobial agents

7 After antimicrobial therapy has been initiated careful attention should be directed to eliminating the possible portal of entry of the causative agent—for example poor dental hygiene or urinary tract infections with or without stones Dentulous patients with IE who are not critically ill should have dental x ray films and an oral surgery consultation so that necessary dental work can be performed *while* the patient is receiving treatment for IE Because of the association with inflammatory bowel disease and carcinoma of the colon patients with IE caused by *Streptococcus bovis* should have a proctoscopy and colon x ray studies while receiving antimicrobial therapy

8 If severe heart failure that is unresponsive to medical therapy ensues before completion of antimicrobial therapy prompt cardiac valve replacement should be considered Procrastination in an attempt to complete a course of antimicrobial therapy preoperatively will only increase the surgical mortality The hemodynamic status of the patient should be the most important factor in determining the timing of cardiac valve replacement

9 Before dismissal from the hospital patients and their families should receive adequate instructions in prophylactic measures for IE IE often has multiple and complex medical surgical and laboratory facets and patient education concerning prophylaxis is an important although frequently overlooked component

10 Follow up blood cultures should be obtained at 1 and 2 months after completion of antimicrobial therapy Relapses if they occur most often appear within the first 2 months after completion of treatment Infections caused by fungi, *Staphylococcus epidermidis* and fastidious microorganisms such as *Haemophilus* species may relapse later than 2 months

11 Finally physicians should respect the seriousness of IE and should resist the temptation to compromise in the duration and means of administration of therapy or to switch to less effective antimicrobial agents After initiation of therapy some patients with IE especially those with penicillin sensitive streptococcal infections, will experience a dramatic improvement in general well being and disappearance of fever These improvements should not be interpreted as an indication that the antimicrobial may be switched to orally administered agents or that the length of treatment may be shortened Symptomatic control of most hypersensitivity reactions should be attempted before a change is made to alternative therapy If major hypersensitivity reactions or other complications occur which cannot be controlled by symptomatic measures alternative therapy may be used. Clinicians should use only those accepted forms of alterna

Table II Treatment of penicillin sensitive viridans or nonenterococcal group D streptococcal infective endocarditis (MIC ≤ 0.1 μg/ml)

Treatment of patients not allergic to penicillin	*Alternative treatment of patients allergic to penicillin*
Procaine penicillin 1.2 million units IM q6h *plus* streptomycin 7.5 mg/kg IM q12h for 14 days	Cephalothin 1 g IV q4h for 28 days
or	or
Aqueous penicillin 20 million units IV per day for 28 days *plus* streptomycin 7.5 mg/kg IM q12h for the first 14 days of treatment	Vancomycin 7.5 mg/kg IV q6h for 28 days
or	
Aqueous penicillin 20 million units IV per day for 28 days	

Modification of method of Wolfe and Johnson [?]

Table IV Treatment of penicillin sensitive staphylococcal infective endocarditis (MIC ≤ 0.1 µg/ml)

Treatment of patients not allergic to penicillin	*Alternative treatment of patients allergic to penicillin*
Aqueous penicillin G 20 million units per day for 4 to 6 weeks	Cephalothin 1 g IV q4h or cefazolin 1 g IV or IM q6h for 4 to 6 weeks or Vancomycin 7.5 mg/kg IV q6h for 4 to 6 weeks

from nonenterococci (*S bovis*) by their growth in broth containing 6 5% sodium chloride

A very important characteristic of enterococci is that they are inhibited but not killed by penicillin alone A combination of penicillin (or ampicillin carbenicillin or ticarcillin) and aminoglycosides (streptomycin kanamycin gentamicin tobramycin or amikacin) acts synergistically against enterococci, and combined treatment is necessary for the successful therapy of enterococcal IE [illegible]

Table III outlines standard antimicrobial therapy for enterococcal IE Moellering and associates and others have shown that only about 60% of enterococci show synergy of bactericidal effect when incubated with penicillin plus streptomycin compared with penicillin alone [illegible] The approximate 40% of strains which are highly resistant to streptomycin (MIC > 2 000 µg/mL) do not show this synergistic effect The combined use of penicillin and gentamicin has been shown to result in synergistic bactericidal effect in vitro against most enterococci, including strains that are highly resistant to streptomycin Additionally combinations of penicillin and tobramycin ampicillin and gentamicin and vancomycin and gentamicin were found to act synergistically in vitro against highly streptomycin resistant strains of enterococci Hook and associates and Carrizosa and Kaye demonstrated in the experimental rabbit model of IE that the combination of penicillin and gentamicin was superior to the combination of penicillin and streptomycin in the treatment of infection caused by highly streptomycin resistant enterococci

The significance of streptomycin resistance in human IE is not clear At present insufficient data exist to indicate conclusively the s[illegible] of the penicillin gentamicin combination [illegible] penicillin streptomycin combination [illegible] treatment of streptomycin resistant entero[illegible] IE In patients with infections caused by [illegible] mycin resistant microorganisms, o[illegible] course might be to initiate therapy with [illegible] plus streptomycin and then measure the SBT [illegible] the SBT is low (<1 8) the dosage of [illegible] could be increased from 20 million units p[illegible] to 40 million units per day and the SBT [illegible] be remeasured If the SBT is still less th[illegible] gentamicin could be substituted for strep[illegible] and the SBT could be rechecked again [illegible] could then be made concerning the relat[illegible] apeutic advantage of streptomycin or g[illegible]cin

Some patients with enterococcal IE [illegible] require simultaneous antistaphylococcal th[illegible] for unrelated infections. In other [illegible] patients with acute IE such as that in [illegible] addicts may require initial antimicrobial th[illegible] for IE caused by either staphylococci or ent[illegible] cocci. In vitro studies have demonstrated [illegible] with nafcillin or oxacillin plus gentamicin [illegible] some strains of enterococci [illegible] However [illegible] and associates [illegible] in the experimental [illegible] model demonstrated that combinatio[illegible] cillinase resistant penicillin and gentamicin [illegible] not as effective as penicillin plus strept[illegible] gentamicin in the treatment of exper[illegible] enterococcal IE Until more data are av[illegible] nafcillin oxacillin or methicillin sho[illegible] substituted for penicillin G in the trea[illegible] enterococcal IE Likewise cephalospori[illegible] not be combined with streptomycin or gen[illegible] as a substitute for penicillin in the treatm[illegible] enterococcal IE [illegible] In these patients th[illegible] with three antimicrobial agents (that is pe[illegible] lin streptomycin and nafcillin) would be [illegible]able

Because experience with the use of al[illegible] to penicillin in patients with enterococcal [illegible] limited efforts should be made to con[illegible] use of penicillin in patients who have an e[illegible] history of previous "reaction" to pe[illegible] patients who experience minor hypersens[illegible] reactions during the course of treatment [illegible] penicillin In these patients symptoms [illegible] py may control minor hypersensitivity re[illegible] If penicillin therapy has to be interrupted [illegible]

vas 3% among our 68 patients who were treated with short term intramuscular therapy [21, 44] This is similar to that reported by Tompsett and [43] and by Wolfe and Johnson [4] Streptomycin associated toxicity is more likely to occur in he elderly and in patients who have abnormal renal function Streptomycin should be used with aution if at all in these patients Short term ntramuscular combined therapy should not be used in thrombocytopenic patients or in patients who have severe heart failure shock or other onditions in which there is presumed poor peripheral perfusion and possible decreased absorption of antimicrobial agents from sites of ntramuscular injection

Penicillin sensitive streptococcal IE may also be treated successfully with high dose intrave nous penicillin G alone The treatment should not be less than 4 weeks in duration In earlier clinical rials more than 50% of patients receiving 0 5 to 1 million units of penicillin per day for less than 2 weeks were treatment failures [4] When the losage of penicillin was increased to 14 to 16 million units per day for 10 to 14 days relapse rates of 15% were still encountered In two ecent retrospective studies no relapses occurred patients treated for 4 weeks or more with igh dose parenteral penicillin alone [5]

Based on data currently available it appears that the three regimens outlined above and in Table II are roughly equivalent in their cure rate The advantages of treatment for 2 weeks with ntramuscular antimicrobials over treatment for 4 weeks with intravenous antimicrobials or combined intramuscular and intravenous therapy or 4 weeks however are clear—namely short ned hospitalization period with reduced cost to patients more efficient use of hospital personnel and facilities and avoidance of potentially hazardous complications associated with the use of intravenous therapy A disadvantage of combined therapy is the small risk of streptomy cin associated vestibular toxicity This toxicity may be minimized by restricting the use of strep omycin in patients 65 years old or older or in patients with abnormal renal function and by ollowing patients closely for signs of developing estibular dysfunction Elderly patients and patients who have abnormal renal function hould be treated with penicillin G alone Anoth r disadvantage to the use of short term combined intramuscular therapy is the frequent intramuscular injections that are necessary In

Table III Treatment of penicillin resistant (enter ococcal) infective endocarditis (MIC $\geqq$ 0 1 µg/ ml)

Treatment of patients not allergic to penicillin	*Alternative treatment of patients allergic to penicillin*
Penicillin 20 to 40 million units IV per day or ampi cillin 12 g IV per day *plus* Streptomycin 7 5 mg/kg IM q12h or gentamicin 1 mg/kg IM or IV q8h for 4 to 6 weeks	Vancomycin 7.5 mg/kg IV q6h *plus* Streptomycin 7.5 mg/kg IM q12h or gentamicin 1 mg/kg IM or IV q8h for 4 to 6 weeks or Desensitize to penicillin

our experience however the intramuscular injec tions were generally well tolerated The tolerance was enhanced somewhat when the patient under stood that with this form of therapy mobility in the hospital is increased and the period of hospi talization is decreased

In patients who are unable to take penicillin because of hypersensitivity cephalosporins should be used with caution because of the possi bility of cross sensitivity reaction Cephalothin and vancomycin have been used successfully in the treatment of viridans and nonenterococcal group D streptococcal infections [3] [5] Desen sitization of patients to penicillin should be attempted only when alternative forms of thera py are impractical or unavailable

Until more data are available treatment of IE caused by other penicillin sensitive streptococci such as group A beta hemolytic streptococci group B streptococci *Streptococcus pneumoniae* and the like should be with high-dose penicillin (20 million units per day) intravenously for 1 month Patients who are unable to take penicillin may be treated for 1 month with cephalothin or vancomycin in dosages outlined in Table II

Penicillin resistant streptococcal IE—enterococci (MIC $\geqq$ 0 1 µg/ml)

The group D streptococci enterococcus group contains the organisms *S fecalis* and its two variants (zymogenes and liquefaciens) *S fae cium* and *S durans* Almost all of the enterococci that cause IE are *S fecalis* and most of these are of the variety liquefaciens Group D streptococci may be distinguished from viridans streptococci by their ability to grow in media containing bile and the enterococci may be further distinguished

authors have expressed doubts about the usefulness of cefazolin in the treatment of human IE due to S aureus[84] However, most clinicians believe that methicillin oxacillin nafcillin, cephalothin and cefazolin are roughly equivalent in their efficacy in the treatment of patients with IE due to S aureus Vancomycin may be used in patients who are unable to tolerate penicillin or cephalosporins

Table V outlines accepted antimicrobial therapy in patients with penicillin resistant staphylococcal IE Sabath and associates[85] recently describes staphylococci that are inhibited by low concentrations but are not killed by high concentrations of penicillinase resistant penicillins This disparity between MIC and MBC known as tolerance is of uncertain clinical significance More clinical experience is needed before conclusions can be made regarding the need for different therapeutic approaches to these patients with tolerant S aureus infections

The treatment of patients with endocarditis caused by penicillinase resistant S aureus is somewhat controversial That the antimicrobial therapeutic regimen should include a penicillinase resistant penicillin (nafcillin oxacillin or methicillin) a cephalosporin or vancomycin is unquestioned Controversy surrounds the desirability of the addition of other antimicrobial agents that are synergistic against S aureus when combined with the standard antistaphylococcal agents compared with the activity of penicillins or cephalosporins alone Sande and Johnson[89] demonstrated that the combination of penicillin and gentamicin acted synergistically in vitro against a strain of penicillin susceptible S aureus The combination of nafcillin and gentamicin showed synergy in vitro against penicillinase producing S aureus compared with the activity of nafcillin alone [92] In IE due to S aureus in experimental animals the organisms were eradicated more rapidly from cardiac vegetations when animals were treated with the combination of gentamicin and nafcillin than with nafcillin alone[90] Insufficient data exist to suggest that the combination of gentamicin and nafcillin should be used as standard therapy of human IE caused by S aureus The potential increased toxicity of the use of combined treatment should be considered and weighed against the theoretic benefit Gentamicin alone should not be used as therapy for IE due to S aureus

Mutant variants of S aureus emerge in [illegible] mental animals with IE caused by S [illegible] these animals are treated with gentamicin [illegible] and the use of gentamicin fails to steril[illegible] cardiac vegetation[93, 94]

A retrospective study of the use of single [illegible] and combination treatment with gentamic[illegible] patients with IE due to S aureus showed benefit from the use of the combination [illegible] single drug treatment[95] A cooperative prosp[illegible]tive study is currently under way compar[illegible] combination of nafcillin gentamicin therapy [illegible] the use of nafcillin alone in patients with pe[illegible]linase producing IE caused by S aureus

IE caused by methicillin resistant S [illegible] rare and treatment with vancomycin may b[illegible] necessary [illegible] Rifampin in combination with [illegible] antimicrobial agents may also prove useful in [illegible] treatment of methicillin resistant S aureus [illegible]tions[96]

S epidermidis is one of the most com[illegible] agents causing infection in patients with [illegible]thetic heart valves and cerebrospinal [illegible] shunts[9, 97] Whereas methicillin resistant [illegible] of S aureus are rare, S epidermidis resista[illegible] methicillin occurs commonly The freque[illegible] methicillin resistant S epidermidis isolate[illegible] been reported to range from 10 to 63%[illegible] er[101] reported that 63% of 27 isolates from pa[illegible] with prosthetic valve endocarditis or [illegible] cerebrospinal fluid shunts were resista[illegible] methicillin Archer made an extensive study of [illegible] vitro susceptibility and resistance patter[illegible] these 27 isolates Against methicillin res[illegible] isolates vancomycin cephalothin and cefa[illegible]dole had excellent activity against most isola[illegible] Among aminoglycosides tested gentamici[illegible] most active and no resistant cell populations [illegible] identified among susceptible isolates. R[illegible] identified among susceptible isolates [illegible] was the single most active agent against [illegible] isolates but high level resistance to rif[illegible] emerged in some isolates after 8 to 24 hou[illegible] incubation Because of the high frequen[illegible] methicillin resistance the initial regimen [illegible] treatment of IE caused by S epidermid[illegible] include agents that are active against methi[illegible] resistant microorganisms On the basis of [illegible] currently available cephalothin cefam[illegible] cefazolin alone or in combination with [illegible] agents chosen from among vancomycin r[illegible] and gentamicin appears to be the reg[illegible] choice for treatment of IE caused by meth[illegible]

patients subsequent resumption of therapy with penicillin is more likely to provoke serious reactions and alternative therapy should then be instituted In these patients or in patients with a history of anaphylaxis or other major hypersensitivity reaction to penicillin combinations of vancomycin streptomycin or vancomycin gentamicin may be used[6, 8, 77]

Combined penicillin aminoglycoside therapy is effective treatment for enterococcal IE No relapses occurred among 36 patients reported by Mandell and associates[61] and one relapse occurred among 30 patients reported by Geraci and colleagues[8] However adverse reactions associated with the use of aminoglycosides are common The high frequency of adverse and toxic reactions may be in part related to the average older age of patients with enterococcal IE (mean age 60 years) than that of patients with IE caused by other microorganisms (mean age 40 to 50 years)[78] Vestibular disturbances occurred in 10 to 30% of patients treated with streptomycin and 13 of 16 patients (81%) treated with gentamicin had abnormal values for serum creatinine (Wilkowske and associates unpublished data) Ototoxic reactions may also occur with the use of vancomycin and gentamicin Serum concentration of aminoglycosides and vancomycin should be measured frequently throughout the course of treatment Peak serum concentration of streptomycin 1 hour after administration of the dose should be adjusted to 10 to 15 µg/ml and should not exceed 20 µg/ml Peak 1 hour serum concentration of gentamicin should range from 3 to 5 µg/ml Peak 1 hour serum concentration of vancomycin should not exceed 20 µg/ml

Penicillin sensitive staphylococcal IE (MIC ≦ 0 1 µg/ml)

The course of IE caused by staphylococci is often acute and immediate antimicrobial therapy is required Staphylococcal endocarditis should be suspected in illicit intravenous drug abusers patients with prosthetic heart valves and when the suspected portal of entry is cutaneous or is associated with intravenous catheters Because more than 50% of community acquired and more than 80% of hospital acquired staphylococci produce penicillinase initial treatment of suspected staphylococcal IE should include a penicillinase resistant penicillin or a cephalosporin

Table V Treatment of penicillin resistant staphylococcal infective endocarditis (MIC ≧ 0 1 µg/ml)

Treatment of methicillin susceptible S aureus *and* S epidermidis *infections*	
Treatment of patients not allergic to penicillin	*Alternative treatment of patients allergic to penicillin*
Nafcillin oxacillin or methicillin 2 g IV q4h for 4 to 6 weeks	Cephalothin 1 g IV q4h or cefazolin 1 g IV or IM q6h for 4 to 6 weeks or Vancomycin 7.5 mg/kg IV q6h for 4 to 6 weeks
Treatment of methicillin resistant *S epidermidis* infections	
Cephalothin or cefamandole 1 g IV q4h or cefazolin 1 g IV q6h for 4 to 6 weeks	

Combinations of cephalosporins, vancomycin, gentamicin, rifampin may enhance killing of methicillin resistant *S epidermidis*

After the MIC is available only infections caused by staphylococci with penicillin MIC ≦ 0 1 µg/ml should be treated with penicillin G alone *S aureus* strains with penicillin MIC >0 1 µg/ml usually produce penicillinase and the production of penicillinase can be induced by the presence of penicillin Table IV outlines the usual therapeutic programs for IE caused by penicillin sensitive staphylococci A cephalosporin or vancomycin is an acceptable alternative to penicillin in patients who are unable to tolerate penicillin Treatment should be continued for a minimum of 4 weeks

Penicillin resistant staphylococcal IE (MIC ≧ 0 1 µg/ml)

Studies have been performed in experimental animals which have compared the efficacy of the most commonly used penicillinase resistant antistaphylococcal agents Egert and associates[1] reported that methicillin nafcillin and oxacillin were equally effective in experimental rabbit IE Carrizosa and associates[4] found that methicillin reduced more rapidly than did cefazolin or cephalothin the titers of *S aureus* in experimental aortic valve vegetations Cefazolin is more susceptible to inactivation by beta lactamase produced by *S aureus* than is cephalothin[83] and some

therapy is effective We believe that all patients with PVE should receive a minimum of 4 weeks of intravenous therapy with bactericidal antimicrobials

The use of anticoagulant therapy in patients with IE is controversial. Since the report by Thill and Meyer[11] published in 1947 many authorities have affirmed that anticoagulants are contraindicated in cases of endocarditis of natural or prosthetic valves because of the potential risk of central nervous system bleeding after thromboembolism [11-13] Because of the increased risk of thromboembolism with discontinuance of anticoagulant therapy in patients with prosthetic valves it would be desirable to continue the use of anticoagulants in patients with PVE provided that such therapy did not increase morbidity and mortality especially from central nervous system bleeding after thromboembolism We reported earlier that the use of anticoagulants did not increase morbidity or mortality in patients with PVE On the contrary the risk of major clinical central nervous system complications was increased and the mortality rate was higher when anticoagulants were discontinued Central nervous system complications occurred nine times more frequently when anticoagulants were discontinued or given in subtherapeutic dosage than when adequate anticoagulation was continued We believe that carefully controlled anticoagulant therapy should be continued cautiously in patients with PVE Patients should be observed closely for the development of central nervous system complications If such complications occur we agree with Karchmer and associates that use of anticoagulants should be discontinued temporarily If there is no clinical or laboratory evidence of intracranial hemorrhage anticoagulants may be reinstituted

Another difference between patients with PVE and those with natural valve IE is the necessity for a more aggressive surgical approach to patients with PVE We agree with Karchmer and co workers Richardson and associates and Saffle and colleagues that all patients with PVE who have moderate or severe heart failure that is unresponsive to medical therapy or in whom significant paravalvular leaks develop should undergo valve replacement early in the course of their illness Failure to act quickly with surgical intervention in these patients significantly increases the mortality rate The need for early cardiac valve replacement in all patients [illegible] early-onset PVE caused by staphylococ[illegible] been stressed by Richardson and associa[illegible]

The role of cardiac valve replacement in patients with IE

The role of cardiac valve replacem[illegible] patients with PVE and fungal IE has be[illegible] discussed briefly above During the antibi[illegible] congestive heart failure replaced seps[illegible] leading cause of death among patie[illegible] and most patients with IE who experie[illegible] failure do so because of hemodynamic c[illegible] quences of incompetent cardiac valves ex[illegible] bated by valvular infection In a retrosp[illegible] analysis of patients who underwent cardia[illegible] replacement because of heart failure caused b[illegible] IE we found the operative mortality to be d[illegible] related to the degree of functional heart fa[illegible] present at the time of operation [illegible] compared with a similar group of patients [illegible] IE who underwent cardiac valve replaceme[illegible] operative mortality was remarkably simi[illegible] that of patients with IE when the degree of [illegible] failure was the same at the time of [illegible] both groups of patients

In patients with functional Class IV [illegible] failure or with sudden-onset severe aortic [illegible] ciency associated with IE urgent cardia[illegible] replacement probably offers the only [illegible] survival. Cardiac valve replacement [illegible] successfully performed in these patients [illegible] active infection even when blood cul[illegible] positive in the immediate preoperative peri[illegible] Procrastination in cardiac valve replace[illegible] these patients in an attempt to stabi[illegible] failure by medical therapy [illegible] course of antimicrobial therapy [illegible] usually results in death from cardiac f[illegible] believe that the hemodynamic status of p[illegible] with IE should be the determining factor [illegible] timing of cardiac valve replacement rather [illegible] the activity of infection or the length of p[illegible] ative antimicrobial therapy

Richardson and associates sugges[illegible] patients with IE due to *S aureus* should [illegible] cardiac valve replacement We agree w[illegible] port that not all patients with IE caused [illegible] *aureus* require cardiac valve replacement [illegible] experience some patients with IE caused [illegible] *aureus* especially those with tricuspid [illegible] can be treated successfully with medical [illegible]

esistant *S epidermidis* The optimal combina ion of agents would depend on the results of in itro tests of MBC and SBT and of synergy tudies Until further data are available infec ions caused by methicillin *susceptible* strains of *S epidermidis* are probably best treated with a ingle agent (oxacillin nafcillin methicillin or ephalosporin)

The semisynthetic penicillins and cephalospo ins are generally well tolerated but adverse and oxic reactions occur Methicillin associated renal ailure and interstitial nephritis have been well locumented [°, 91] Other adverse reactions asso iated with the use of semisynthetic penicillins ave been granulocytopenia and hepati is [8, 10] Use of a cephalosporin may be asso iated with neutropenia and occasional renal ailure [106]

The mortality rate associated with staphylo occal IE is high The prognosis among heroin ddicts is relatively more favorable than that mong nonaddicts [95, 10, 10] The mortality rate of taphylococcal IE among nonaddicts usually xceeds 50% [6, 87, 109] Poor prognosis has been ssociated with an age of more than 50 years and he presence of underlying diseases—cardiac lisorders alcoholism cirrhosis and diabetes nellitus The rate of survival from staphylococcal ndocarditis is higher if the patient lives long nough to receive at least 2 weeks of antimicro ial therapy

Treatment of IE caused by other microorganisms

The antimicrobial therapy of IE caused by ther microorganisms depends on isolation and lentification of the offending organism and the esults of in vitro susceptibility tests of MIC ABC and SBT Susceptibility testing may be ifficult or impossible with some fastidious gram egative bacilli especially *Haemophilus* species Most *Haemophilus* species are highly susceptible o ampicillin and IE caused by these microorgan isms may be treated successfully with ampicillin dministered intravenously for 3 weeks If in vitro usceptibility tests with this organism cannot be erformed empiric therapy with ampicillin or moxicillin may be used Clinical parameters uch as disappearance of fever and return of ppetite serve as guidelines to the effectiveness of herapy in such cases Infections caused by micro rganisms other than those streptococci staphy lococci and *Haemophilus* species described above should be treated a minimum of 4 weeks Most authorities believe that patients with culture negative IE should be treated with regimens that are effective against enterococcal IF [2]

Fungal endocarditis

Candida species and *Aspergillus* species are the most common causes of fungal IE Of the two IE due to *Candida* occurs more commonly and is seen most frequently in association with drug addicts [1] IE caused by *Aspergillus* occurs most often as a complication of cardiac valve replacement [30, 9, 91] The course of fungal endocar ditis is usually subacute or chronic and is charac terized by the frequent occurrence of arterial embolization of large friable fungal vegetations Treatment of fungal IE with amphotericin B or 5-fluorocytosine or both is frequently unsuccess ful and antifungal therapy combined with cardiac valve replacement is necessary in most cases [8, 3]

Prosthetic valve endocarditis

During the past 7 years prosthetic valve endo carditis (PVE) accounted for approximately 17% of the total number of cases of IE seen at the Mayo Clinic Because of differences in microbio logic causation expression of clinical syndrome treatment and prognosis patients with PVE should be considered separately from patients with natural valve endocarditis Infections that occur early (less than 2 months after operation) are most often caused by *S epidermidis S aureus* gram negative bacilli or diptheroids and are associated with a very high mortality rate—more than 80% [3] Late onset infections (more than 2 months after operation) are asso ciated with a better prognosis—38% mortality rate in one study—than early onset infection and are caused by those microorganisms that most often cause natural valve endocarditis

The antimicrobial therapy of patients with PVE is similar to that of patients with natural valve IE One major exception however is the treatment of patients with penicillin sensitive streptococcal PVE These patients should not be treated with short term intramuscular therapy In our experience 4 weeks of intravenous aqueous penicillin G 20 million units per day for 4 weeks combined with streptomycin 7 5 mg /kg intra muscularly every 12 hours for the first 2 weeks of

36 Parker M T and Ball L C Streptococci and aerococci associated with systemic infection in man J Med Microbiol. 9 275 1976
37 Watanakunakorn, C *Streptococcus bovis* endocarditis Am. J Med 56 256 1974.
38 Moellering R C Jr Watson B K. and Kunz L. J Endocarditis due to group D streptococci Comparison of disease caused by *Streptococcus bovis* with that produced by the enterococci Am J Med. 57 239 1974
39 Harder E J Wilkowske C J Washington J A II and Geraci, J E *Streptococcus mutans* endocarditis Ann. Intern Med. 80 364 1974
40 Hunter T H The treatment of some bacterial infections of the heart and pericardium Bull. N Y Acad. Med 28 213 1952.
41 Duperval R Bill, N J Geraci, J E and Washington J A., II Bactericidal activity of combinations of penicillin or clindamycin with gentamicin or streptomycin against species of viridans streptococci, Antimicrob Agents Chemother 8 673 1975
42. Wolfe J C., and Johnson W D Jr Penicillin sensitive streptococcal endocarditis In vitro and clinical observations on penicillin streptomycin therapy Ann Intern Med. 81 178 1974
43. Durack, D T and Petersdorf R G Chemotherapy of experimental streptococcal endocarditis. I Comparison of commonly recommended prophylactic regimens J Clin Invest 52 592 1973
44. Pelletier L. L. Jr., and Petersdorf R G Chemotherapy of experimental streptococcal endocarditis V Effect of duration of infection and retained intracardiac catheter on response to treatment J Lab Clin Med 87 692 1976
45 Sande M A., and Irvin R G Penicillin amino glycoside synergy in experimental *Streptococcus* viridans endocarditis J Infect Dis 129 572 1974
46 Hunter T H and Paterson P Y Bacterial endocarditis D M Nov 1956 p 1
47 Tompsett R., Robbins W C., and Berntsen, C Jr Short term penicillin and dihydrostreptomycin therapy of streptococcal endocarditis Results of the treatment of thirty five patients Am J Med 24 57 1958
48 Wilson W R Geraci J E., Thompson R L., Wilkowske C J and Giuliani, E R Treatment of penicillin-sensitive streptococcal infective endocarditis (PSSIE) with short term intramuscular (IM) procaine penicillin and streptomycin (PP&S) *in* Eighteenth Interscience Conference on Antimicrobial Agents and Chemotherapy Washington D C 1978, American Society for Microbiology Abstract No 276
49 Geraci J E and Martin W J Antibiotic therapy of bacterial endocarditis IV Successful short term (two weeks) combined penicillin-dihydrostreptomycin therapy in subacute bacterial endocarditis caused by penicillin-sensitive streptococci, Circulation 8 494 1953
50 Geraci, J E Further experiences with short term (2 weeks) combined penicillin-streptomycin therapy for bacterial endocarditis caused by penicillin sensitive streptococci. Proc Staff Meet Mayo Clin 30 192, 1955
51 Geraci, J E The anti[illegible] therapy of bacterial endocarditis Therap[illegible] patients seen from 1951 through [illegible] observations on short term therapy (tw[illegible] penicillin sensitive streptococcal endocarditis M[illegible] North Am July 1958 p 1101
52. Phair J P., and Tan J [illegible] of *Streptococcus viridans* endocarditis, *in* Kaplan E L and Taranta A V., editors Infective endocarditis (AHA Monograph 52) Dallas 1977 American Heart Associ[illegible] 55
53 Tompsett, R. and Hurst, M L. Bacterial endocar[illegible] Selected aspects of treatment Trans. Am Cl[illegible] tol. Assoc 83 95 1972.
54 Cates J E and Christie R V Subacute ba[illegible] endocarditis A review of 44[illegible] patients treated [illegible] centres appointed by the Penicillin Trials Com[illegible] the Medical Research Council, Q J Med. [illegible] 1951
55 Christie R V Subacute bacterial endocar[illegible] Med J 2 438 1953
56 Hamburger M and Stein L. Streptococcus [illegible] subacute bacterial endocarditis Two week treat[illegible] schedule with penicillin J A.M.A. 149 54[illegible]
57 Karchmer A W., Moellering R. C Jr Maki, D [illegible] Swartz M N Single antibiotic therapy of [illegible] cal endocarditis (SE) *in* Seventeenth Intersci[illegible] ference on Antimicrobial Agents and Chemo[illegible] Washington D C., 1977 American Society for M[illegible] biology Abstract No 238
58 Hoppes W L. Smith, J W., Lerner P L, and [illegible] A Treatment of penicillin-sensitive strep[illegible] endocarditis (PSSE) *in* Seventeenth Intersci[illegible] ference on Antimicrobial Agents and Chem[illegible] Washington D C 1977 American Society for M[illegible] biology Abstract No 239
59 Friedberg C K., Rosen, K M and Bienstock, [illegible] Vancomycin therapy for enterococcal and S[illegible] *cus viridans* endocarditis Successful treatm[illegible] patients Arch Intern Med. 122 134, 1968
60 Rahal J J Jr., Meyers, B R. and W[illegible] Treatment of bacterial endocarditis with cepha[illegible] N Engl. J Med 279 1305 1968
61 Fekety F R Jr and Weiss I Antibiotic [illegible] Enhanced susceptibility of enterococci to comb[illegible] of streptomycin and penicillins or cephalo[illegible] Antimicrob Agents Chemother 1965 p 156
62 Wilkowske C J Facklam R R. Washington J [illegible] and Geraci, J E Antibiotic synergism [illegible] susceptibility of group D streptococci to certa[illegible] biotic combinations Antimicrob Agents Che[illegible] 1970 p 195
63 Mandell, G L. Kaye D Levison M. E., and [illegible] E W Enterococcal endocarditis An anal[illegible] patients observed at the New York Hospital-Co[illegible] Medical Center Arch. Intern. Med 125 [illegible]
64 Moellering R C Jr Wennersten C., and W[illegible] A. N Synergy of penicillin and gentamicin [illegible] enterococci, J Infect. Dis 124(Suppl.) S20 1971
65 Moellering R C., Jr Wennersten C Medrek, T [illegible] Weinberg A. N Prevalence of high level resist[illegible] aminoglycosides in clinical isolates of ent[illegible] Antimicrob Agents Chemother 1970 p 335
66 Standiford H D de Maine J B and Kirby W [illegible] Antibiotic synergism of enterococci Rela[illegible] tory concentrations, Arch. Intern. Med. 126 [illegible]
67 Moellering R C., Jr., Wennersten C and W[illegible] A J Penicillin tobramycin synergism [illegible] cocci A comparison with penicillin and ge[illegible] Antimicrob Agents Chemother 3 526 1973
68 Harwick, H J Kalmanson G M and Guze L [illegible] vitro activity of ampicillin or vancomycin comb[illegible] with gentamicin or streptomycin against e[illegible] Antimicrob Agents Chemother 4 383, 1973
69 Watanakunakorn C., and Bakie C S[illegible] vancomycin gentamicin and vancomycin strept[illegible] against enterococci, Antimicrob Agents Chemother 4 120 1973
70 Hook E. W., III Roberts R B and S[illegible]

nent alone These patients should be followed losely and if heart failure or other signs of hemodynamic deterioration appear considera ion should be given to urgent cardiac valve eplacement

In general the same guidelines for cardiac alve replacement in the usual population apply o drug addicts A special situation exists in drug addicts who have recurrent infection of the tricus id valve with gram negative bacilli that are esistant to multiple drugs notably *Serratia narcescens* and *Pseudomonas* species In these ts excision of the tricuspid valve without mmediate artificial valve replacement may be necessary[1 8] Although progressive right sided heart failure may subsequently develop in these patients some patients have tolerated the absence of a tricuspid valve for a surprisingly long ime

EFERENCES

1 Wilson W R, and Washington J A II Infective endocarditis—a changing spectrum? (Editorial) Mayo Clin Proc 52 254 1977
2 Kaye D Infective endocarditis, Baltimore 19 6 University Park Press p 47
3 Lerner P I and Weinstein L Infective endocarditis in the antibiotic era N Engl J Med 274 199 259 323 388 1966
4 Tompsett R Bacterial endocarditis Changes in the clinical spectrum Arch. Intern Med 119 329 1967
5 Shinebourne E A Cripps C M Hayward G W and Shooter R A Bacterial endocarditis 1956-1965 Analysis of clinical features and treatment in relation to prognosis and mortality Br Heart J 31 536 1969
6 Bennett I L Jr and Beeson P B Bacteremia A consideration of some experimental and clinical aspects Yale J Biol. Med 26 241 1954
7 Beeson P B Brannon E S and Warren J V Observations on the sites of removal of bacteria from the blood in patients with bacterial endocarditis, J Exp Med 81 9 1945
8 Hook, E W Annotation Yale J Biol Med 38 521 1966
9 Werner A S Cobbs C G Kaye D and Hook E W Studies on the bacteremia of bacterial endocarditis JAMA 202 199 1967
10 Weiss, H and Ottenberg R Relation between bacteria and temperature in subacute bacterial endocarditis J Infect Dis 50 60 1932
11 Wright H D The bacteriology of subacute infective endocarditis J Pathol Bacteriol 28 541 1925
12 Salazar Mallén M Lozano Hube E and Brenes, M Comparative study of blood cultures made from artery vein and bone marrow in patients with subacute bacterial endocarditis AM HEART J 33 692, 1947
13 Sande M A Levison M E Lukas, D S and Kaye D Bacteremia associated with cardiac catheterization N Engl J Med 281 1104 1969
14 Belli, J and Waisbren, B A The number of blood cultures necessary to diagnose most cases of bacterial endocarditis Am J Med Sci 232 284 1956
15 Merchant R K Louria D B Geisler P H Edgcomb J H and Utz J P Fungal endocarditis Review of the literature and report of three cases Ann Intern Med 48 242 1958
16 Derby B M Coolidg K and Rogers D E *Histoplasma capsulatum* endocarditis with major arterial embolism Report of an apparent recovery Arch. Intern Med 110 63 1962.
17 Segal C Wheeler C G and Tompsett R *Histoplasma* endocarditis cured with amphotericin N Engl J Med 280 206 1969
18 Carrizosa J Levison M E, Lawrence T and Kaye D Cure of *Aspergillus ustus* endocarditis on a prosthetic valve Arch. Intern Med 133 486, 1974
19 Kammer R B and Utz J P *Aspergillus* species endocarditis The new face of a not so rare disease Am J Med. 56 506 19 4
20 Washington J A II Laboratory procedures in clinical microbiology Boston 1974 Little Brown & Company
21 Wilson W R Geraci J E Wilkowske C J and Washington J A II Short term intramuscular therapy with procaine penicillin plus streptomycin for infective endocarditis due to viridans streptococci Circulation 57 1158 1978
22 Hook E W and Guerrant R L Therapy of infective endocarditis, *in* Kaye D editor Infective endocarditis, Baltimore 1976 University Park Press p 167
23 Loewe S The problem of synergism and antagonism of combined drugs Arzneim Forsch 3 285 1953
24 Lacey B W Mechanisms of chemotherapeutic synergy *in* Cowan, S T, and Rowatt E editors The strategy of chemotherapy New York 1958, Cambridge University Press p 247
25 Sabath L D Synergy of antibacterial substances by apparently known mechanisms Antimicrob Agents Chemother 1967 p 210
26 Jawetz, F Combined antibiotic action Some definitions and correlations between laboratory and clinical results Antimicrob Agents Chemother 1967 p 203
27 Slade H D Specific binding of glucosyltransferase by *Streptococcus mutans* and its effect on the adherence of the organism *in* Kaplan E L and Taranta A V, editors Infective endocarditis (AHA Monograph 52) Dallas, 1977 American Heart Association Inc p 14
28 Elliott S D Bacteriaemia and oral sepsis, Proc R Soc Med 32 747 1939
29 Schirger A Martin W J Royer R Q and Needham G M Bacterial invasion of blood after oral surgical procedures J Lab Clin Med 55 376 1960
30 Wilson W R Jaumin P M Danielson G K Giuliani, E R Washington J A, II and Geraci, J E Prosthetic valve endocarditis, Ann Intern Med 82 751 1975
31 Levison M E Pathogenesis of infective endocarditis *in* Kaye D, editor Infective endocarditis, Baltimore 1976 University Park Press, p 34
32 Gould K, Ramirez Ronda C H Holmes, R K, and Sanford J P Adherence of bacteria to heart valves in vitro J Clin. Invest 56 1364 1975
33 Scheld W M Valone J A and Sande M A. Bacterial adherence in the pathogenesis of endocarditis Interaction of bacterial dextran platelets and fibrin J Clin Invest. 61 1394 1978
34 Pelletier L L Jr Coyle M, and Petersdorf R Dextran production as a possible virulence factor in streptococcal endocarditis, Proc Soc Exp Biol. Med 158 415 1978
35 Editorial Bacterial stickiness Lancet 1 716, 1974

Cohen J O., editor The staphylococci, New York 1972, John Wiley & Sons, Inc., pp 535-536
110 Geraci, J E., Wilkowske C J., Wilson, W R., and Washington J A., II *Haemophilus* endocarditis Report of 14 patients, Mayo Clin Proc. 52 209 1977
111 Sapira, J D The narcotic addict as a medical patient, Am. J Med. 45 555 1968
112 Harris, P D., Yeoh, C B., Breault J., Meltzer J., and Katz, S Fungal endocarditis secondary to drug addiction Recent concepts in diagnosis and therapy J Thorac. Cardiovasc. Surg. 63 980 1972
113 Utley J R., Mills, J., Hutchinson, J C., Edmunds, L. H., Jr., Sanderson, R G., and Roe, B B Valve replacement for bacterial and fungal endocarditis A comparative study Circulation 48(Suppl. 3) 42, 1973
114. Thill, C J., and Meyer O O Experiences with penicillin and dicumarol in the treatment of subacute bacterial endocarditis, Am. J Med. Sci. 213 300 1947
115 Kanis, J A The use of anticoagulants in bacterial endocarditis, Postgrad Med J 50 312, 1974
116 Ziment, I Nervous system complications in bacterial endocarditis, Am. J Med. 47 593 1969
117 Johnson W D., Jr., Prosthetic valve endocarditis, *in* Kaye D., editor Infective endocarditis, Baltimore 1976, University Park Press, p 137
118 Duvoisin, G E., Brandenburg, R O., and McGoon, D C Factors affecting thromboembolism associated with prosthetic heart valves, Circulation 35(Suppl. 1) 70, 1967
119 Yeh, T J., Anabtawi, I N., Cornett V E., and Ellison, R. G., Influence of rhythm and anticoagulation upon the incidence of embolization associated with Starr Edwards prostheses, Circulation 35(Suppl. 1) 77 1967
120 Friedli, B., Aerichide N., Grondin, P., and Campeau L. Thromboembolic complications of heart valve prostheses, AM. HEART J 81 702, 19[illegible]
121 Wilson W R., Geraci, J E., Danielson, G K., Th[illegible]son, R. L., Spittell, J A., Jr Washington, J A., [illegible] Giuliani, E. R. Anticoagulant therapy and central nervous system complications in patients with prosthetic valve endocarditis, Circulation 57 1004, 19[illegible]
122 Karchmer A W., Dismukes, W E Buckley M J [illegible] Austen, W G Late prosthetic valve endocarditis Clinical features influencing therapy Am. J M[illegible] 64 199 1978
123 Richardson, J V., Karp R B Kirklin, J W [illegible] Dismukes, W E. Treatment of infective endocarditis A 10-year comparative analysis, Circulation [illegible] 1978
124. Saffle, J R., Gardner P., Schoenbaum, S C., [illegible] W., Prosthetic valve endocarditis. The case for prompt valve replacement, J Thorac Cardiovasc Surg [illegible] 1977
125 Wilson, W R., Danielson, G K., Giuliani, E R., Washington, J A., II Jaumin, P M and Geraci, J E. Cardiac valve replacement in congestive heart failure due to infective endocarditis, Mayo Clin Proc 54 [illegible] 1979
126 Wilson, W R Danielson G K., Giuliani E R., Washington J A., II Jaumin P M., and Geraci, J E. [illegible] replacement in patients with active infective endocarditis, Circulation 58 585 1978
127 Rapaport, E. The changing role of surgery in the management of infective endocarditis [illegible] Circulation 58 598, 1978
128. Reyes, M P., Palutke W A., Wylin, R F and [illegible] A M., *Pseudomonas* endocarditis in the Detroit Medical Center 1969-1972, Medicine (Baltimore) [illegible] 1973

Antimicrobial therapy of experimental enterococcal endocarditis Antimicrob Agents Chemother 8 564 1975

Carrizosa J and Kaye D Antibiotic synergism in enterococcal endocarditis J Lab Clin Med 88 132 1976

Watanakunakorn C and Glotzbecker C Comparative in vitro activity of nafcillin oxacillin and methicillin in combination with gentamicin and tobramycin against enterococci Antimicrob Agents Chemother 11 88 1977

Glew R H Moellering R C Jr and Wennersten C Comparative synergistic activity of nafcillin oxacillin and methicillin in combination with gentamicin against enterococci Antimicrob Agents Chemother 7 828 1975

Marier R L Joyce N, and Andriole V T Synergism of oxacillin and gentamicin against enterococci, Antimicrob Agents Chemother 8 571 1975

Lincoln L J Weinstein A J Gallagher M and Abrutyn E Penicillinase resistant penicillins plus gentamicin in experimental enterococcal endocarditis Antimicrob Agents Chemother 12 484 1977

Weinstein A. J and Moellering R C Jr Studies of cephalothin Aminoglycoside synergism against enterococci, Antimicrob Agents Chemother 7 522 1975

Westenfelder G O, Paterson P Y Reisberg B E and Carlson G M Vancomycin streptomycin synergism in enterococcal endocarditis JAMA 223 37 1973

Geraci, J E Wilkowske C J and Washington J A II Enterococcal endocarditis Report of 4? cases seen from January 1958 through December 1968 *in* Tenth Interscience Conference on Antimicrobial Agents and Chemotherapy Chicago 1970 American Society of Microbiology Abstract No 71 p 29

Kaye D Infective endocarditis Baltimore 1976 University Park Press p 1

Finland M Changing ecology of bacterial infections as related to antibacterial therapy J Infect Dis 122 419 1970

Egert J Carrizosa J and Kaye D Comparison of methicillin nafcillin and oxacillin in therapy of *Staphylococcus aureus* endocarditis in rabbits J Lab Clin Med 89 1262 1977

Carrizosa J Santoro J and Kaye D Treatment of experimental *Staphylococcus aureus* endocarditis Comparison of cephalothin cefazolin and methicillin Antimicrob Agents Chemother 13 74 1978

Regamey C, Libke R. D Engelking, E R Clarke J T and Kirby W M M Inactivation of cefazolin cephaloridine and cephalothin by methicillin sensitive and methicillin resistant strains of *Staphylococcus aureus* J Infect Dis 131 291 1975

Bryant, R. E and Alford R H Unsuccessful treatment of staphylococcal endocarditis with cefazolin JAMA 237 569 1977

Sabath L D Wheeler N Laverdiere M Blazevic D and Wilkinson B J A new type of penicillin resistance of *Staphylococcus aureus* Lancet 1 443 1977

Kaye D Changes in the spectrum diagnosis and management of bacterial and fungal endocarditis Med Clin North Am 57 941 1973

Watanakunakorn C Tan J S and Phair J P Some salient features of *Staphylococcus aureus* endocarditis, Am J Med 54 473 1973

Masur H Murray H W and Roberts R B Nafcillin therapy for *Staphylococcus aureus* endocarditis Antimicrob Agents Chemother 14 457 1978

89 Sande M A and Johnson M L Antimicrobial therapy of experimental endocarditis caused by *Staphylococcus aureus* J Infect Dis 131 367 1975

90 Sande M A and Courtney K B Nafcillin gentamicin synergism in experimental staphylococcal endocarditis J Lab Clin Med 88 118 1976

91 Watanakunakorn C and Glotzbecker C Enhancement of the effects of anti staphylococcal antibiotics by aminoglycosides Antimicrob Agents Chemother 6 802, 1974

92 Steigbigel R T Greenman R L and Remington J S Antibiotic combinations in the treatment of experimental *Staphylococcus aureus* infection J Infect Dis 131 245 1975

93 Wilson S G and Sanders, C C Selection and characterization of strains of *Staphylococcus aureus* displaying unusual resistance to aminoglycosides Antimicrob Agents Chemother 10 519 1976

94 Miller M H Wexler M A, and Steigbigel, N H Single and combination antibiotic therapy of *Staphylococcus aureus* experimental endocarditis Emergence of gentamicin resistant mutants Antimicrob Agents Chemother 14 336 1978.

95 Watanakunakorn C and Baird I M Prognostic factors in *Staphylococcus aureus* endocarditis and results of therapy with a penicillin and gentamicin Am J Med. Sci 273 133 1977

96 Jensen K Methicillin resistant staphylococci (Letter to the Editor) Lancet 2 1078 1968

97 Dismukes W E Karchmer A W, Buckley M J, Austen W G and Swartz M. N Prosthetic valve endocarditis Analysis of 38 cases Circulation 48 365 1973

98 Slaughter L, Morris, J E, and Starr A Prosthetic valvular endocarditis A 12 year review Circulation 47 1319 1973

99 Schoenbaum S C Gardner P and Shillito J Infections of cerebrospinal fluid shunts Epidemiology clinical manifestations and therapy J Infect Dis 131 543 1975

100 Sabath L D Barrett F F Wilcox C Gerstein D A and Finland, M Methicillin resistance of *Staphylococcus aureus* and *Staphylococcus epidermidis* Antimicrob Agents Chemother 1968 p 302

101 Archer G L Antimicrobial susceptibility and selection of resistance among *Staphylococcus epidermidis* isolates recovered from patients with infections of indwelling foreign devices, Antimicrob Agents Chemother 14 353 1978

102 Baldwin D S Levine B B McCluskey R T and Gallo G R Renal failure and interstitial nephritis due to penicillin and methicillin N Engl J Med 279 1245 1968

103 Ditlove J Weidmann P Bernstein M and Massry S G Methicillin nephritis, Medicine (Baltimore) 56 483 1977

104 Markowitz S M Rothkopf M, Holden F D Stith, D M and Duma, R J Nafcillin induced agranulocytosis, JAMA 232 1150 1975

105 Dismukes W E Oxacillin induced hepatic dysfunction JAMA 226 861 1973.

106 Appel G B and Neu H C The nephrotoxicity of antimicrobial agents N Engl. J Med 296 663 722 784 1977

107 Banks T Fletcher R and Ali, N Infective endocarditis in heroin addicts, Am J Med. 55 444 1973

108 Menda K B and Gorbach, S L Favorable experience with bacterial endocarditis in heroin addicts Ann Intern Med 78 25 1973

109 Eickhoff T C Therapy of staphylococcal infection *in*

stellate ganglionectomy preceding an experimental coronary occlusion reduced the incidence of acute cardiac deaths, indeed, in two groups of ten dogs each ventricular fibrillation occurred in five neurally intact animals but in only one previously sympathectomized dog In addition the authors advanced the remarkable hypothesis that the nervous pathways which carry the painful impulses in angina may perhaps act as a reflex arc which carries pain and other impulses to the heart which are deleterious to its function [7] A recent and appreciable review[8] pointed out that Cox and Robertson s data if analyzed according to current criteria fail to attain statistical significance Had those authors known the future fashion of a p value they would have certainly performed two more experiments for the sake of a p value $< 0\ 05$

Myocardial ischemia and autonomic disturbance The work by Pantridge s group[9, 10] represents a clinical milestone It was found that the vast majority of patients had signs of autonomic disturbance within the first 30 minutes from the onset of acute myocardial infarction, signs of excessive sympathetic activity were more frequent in cases of anterior infarction whereas signs of vagal overactivity were more frequent in inferior infarctions Thus it was suggested that different specific mechanisms likely to be neural were involved in either anterior or inferior infarctions independently of common denominators such as pain emotion or pump failure

a Increased efferent sympathetic activity Classically an increased sympathetic activity in the course of a visceral disease is thought to result from brain mechanisms like pain and emotion or from peripheral reflex influences

The work by Littler and associates[11] on direct arterial pressure and electrocardiograms recorded in ambulatory patients with angina pectoris showed that electrocardiographic changes typical of ischemic attacks can be accompanied by hypertension and tachycardia before the onset of pain The literature associating angina and increases in arterial pressure and heart rate is extremely abundant however the novelty of that report was that pressor events were independent of emotion and pain and therefore the most likely cause was a pressor reflex from the heart This hemodynamic picture has been particularly well documented in the more recent studies by Maseri s group[12]

There is increasing evidence that excitation of afferent fibers from the heart traveling in the cardiac sympathetic nerves may have an important role in determining the reflex sympathetic activity returning to the heart and affecting cardiac events these reflexes can be properly defined as cardio cardiac sympathetic reflexes[14 16] The excitation of cardiac sympathetic afferent fibers is also capable of reflexly inhibiting the activity of efferent vagal cardiac fibers through a sympatho vagal reflex[1] Thus the excitation of sympathetic cardiac afferent fibers could affect the heart and stimulate its function through an increased sympathetic discharge and a synergistically reduced vagal restraint

Cardiac sympathetic sensory endings, subserved by myelinated[18] or unmyelinated fibers[1] are mechanoreceptors normally excited by mechanical events[18 19] but their activity can be further enhanced by chemical substances like bradykinin[20] which are known to be released in the ischemic heart The hypothesis is that mechanical abnormalities of the ischemic myocardium and chemical factors possibly in sequence underlie a crescendo excitation of spontaneously active sympathetic afferent fibers leading to pressor reflexes and above a given threshold to pain When pain supervenes in the course of a cl... ischemic episode a further rise in arterial pressure usually occurs[11 13]

This sympathetic overactivity could have in principle opposite consequences On the one hand it might beneficially attempt to maintain normal ventricular function through an increased contractility[21] thus opposing ventricular dilatation and vagally mediated depressor reflexes On the other hand deleterious effects are strongly suggested by numerous facts The traditional view is that an increased sympathetic activity profoundly alter the balance between oxygen supply and demand especially in the jeopardized myocardium In electrophysiological terms it would increase the electrical inhomogeneity which already results from cellular damage through mechanisms of altered automaticity and dispersion of the refractory period

That sympathetic cardio cardiac reflexes may influence occurrence of arrhythmias in the ischemic heart has recently been demonstrated in experimental animals The interruption of the afferent sympathetic limb of the cardio-cardiac reflex by a section of dorsal roots from the ...

\eural mechanısms ın lıfe threatenıng

ı ıı

\lberto Mallıanı M D
'eter J Schwartz M D
\lberto Zanchettı M D
ı Italy

\rrhythmıas may be due to abnormalıtıes of ıutomatıcıty of conductıon or to a combınatıon ıf both[1] The vısceral nervous system through ıts ympathetıc and parasympathetıc outflows can nodıfy both of these propertıes and quıte com ılex ınteractıons are lıkely to occur

Dısturbances ın cardıac rhythm are quıte com non but there ıs a major dıfference between enıgn and lıfe threatenıng arrhythmıas

It ıs currently held[2,3] that any condıtıon ncreasıng the electrıcal ınhomogeneıty of cardıac nuscle renders ıt more vulnerable to arrhythmo enıc mechanısms ıncludıng the autonomıc nfluences Indeed ıt seems lıkely that some lectrıcal ınhomogeneıty should be necessary ıther orıgınatıng ın the myocardıum ıtself or due o ınhomogeneıty ın the ınfluences playıng upon † to create those condıtıons usually assocıated ıth lıfe threatenıng arrhythmıas

It ıs the purpose of thıs brıef revıew to analyze ome clınıcal and pathophysıologıcal states often haracterızed by lethal arrhythmıas and ın whıch utonomıc mechanısms seem to play a major role hıs role ın the dıfferent condıtıons ıs lıkely to ange from what seems to be an aggravatıng ıctor as occurs durıng acute myocardıal ısche ııa to what seems to constıtute a more substan ıal pathogenetıc mechanısm or at least a crucıal rıgger as ıs the case of the long QT syndrome

In thıs revıew the underlyıng cellular electro physıology wıll be only alluded to whıle emphasıs wıll be placed on the over all autonomıc ınfluences ın an attempt to analyze the genesıs of theır changes and the role of theır effects ın the occurrence of lıfe threatenıng arrhythmıas On the basıs of thıs analysıs we shall also advance some logıcal therapeutıc ımplıcatıons

1 Neural mechanısms ın arrhythmıas assocıated wıth myocardıal ıschemıa

It was the merıt of surgeons to have fırst apprecıated that some crucıal ınteractıon could occur between myocardıal ıschemıa and the nerv ous system to cause lethal arrhythmıas Indeed thıs concept happened to develop durıng the attempts at solvıng another problem that of the relıef of angınal paın Apparently Françoıs Franck ın 1899 proposed a cervıco thoracıc sym pathectomy for the ınterruptıon of the nocıcep tıve path from the heart (quoted by Danıelopo lu)

In 1916 Jonnesco followed that suggested but the ınterventıon was judged physıologıquement ınadmıssıble by Danıelopolu[4] as ın hıs opınıon ıt would also ınterrupt the efferent cardıac sym pathetıc supply thought to be a vasodılator of the coronary arterıes thus enhancıng the rısk of coronary spasm then as fashıonable as nowadays Lerıche and co workers shared for some years Danıelopolu s vıew but eventually felt as a result of both clınıcal and experımental work that a hıgh thoracıc sympathectomy could be benefıcıal ın cases of angına pectorıs as such a procedure seemed to attenuate the tendency to ventrıcular fıbrıllatıon

A few years later ın 1936 Cox and Robertson stressed agaın on much better grounds that

›m the I tıtuto R cerch Card ascol ıı d Istıtuto Patologıa ›dıca I, Unı ers ty f Mılan and Centro R h Cardıovascoları \R, Mılan Italy

c ı ed for publ catıon Aug 15 19 9

print requests Dr Alberto Mallıan Istıt t R c che Card o asco ı e I tıtuto Patol gıa Med c I U ı ers ta d Mı lano Mı n ıly

)0?-8ı03/80/110 05 + 11$01 10/0 © 1980 The C V Mosby Co

arrhythmias are the experiments performed by Verrier Lown and their associates[39,40] They found that hypothalamic stimulation not only promotes fibrillation in animals with acute myocardial ischemia[39] but also lowers the threshold for ventricular fibrillation in intact animals[40] These effects on ventricular vulnerability could be obtained in vagotomized animals independently of changes in heart rate or in blood pressure, thus they were mediated by changes in sympathetic activity

Electrical stimulation applied directly to the nerves going to the heart has also yielded a considerable amount of information Stimulation of the stellate ganglia lowers the threshold for ventricular fibrillation decreases ventricular refactoriness and may produce ventricular arrhythmias

However information obtained using the technique of electrical stimulation although valuable in identifying neural circuits and in showing the effects of a massive activation of nerve fibers present in the stimulated nerves should be interpreted with caution because of the artificial nature of the stimulus A useful way to integrate these notions is to study the effects of denervation which explores the importance of the continuos neural activity of vagal and sympathetic nerves This goal was initially achieved by studying the effects of bilateral stellectomy recently also unilateral stellectomy has been employed with partly unexpected results For instance among other effects bilateral stellectomy increases the threshold for ventricular fibrillation on the other hand while left stellectomy is attended by a major increase in the ventricular fibrillation threshold right stellectomy paradoxically results in a striking fall in the threshold The antifibrillatory effect of left stellectomy has potentially profound clinical implications and will be further discussed in the section on therapy The paradoxical arrhythmogenic effects of right stellectomy have been now repeatedly confirmed in several experimental conditions

The role of vagal activity in ventricular arrhythmogenesis is still unclear The traditional view that the vagus exerts little or no influence on ventricular electrical properties was initially challenged by Kent and Epstein who found that vagal stimulation significantly increased the threshold for ventricular fibrillation in both the
normal and the ischemic myocardium
quently Verrier and associates found th
activation exerts a protective effect wh
sympathetic activity is elevated and is
without effect when the adrenergic input
heart is largely prevented by beta adre
blockade A possible basis for this ir er
would be represented by an activation of
rinic presynaptic receptors modulatin
lease of catecholamines The most likely
tomic site for the interaction is the His-Pu
system which is richly innervated by vag
sympathetic neuroeffector endings. The m
lar basis for this adrenergic-cholinergic
nism has recently been indicated by Wat
and Besch[53] as possibly being mediated by
AMP cyclic GMP interactions

However, a correct understanding of
vagal effects on arrhythmias is made diffic
the fact that changes in vagal activity are a
panied by profound changes in heart rate
very importantly influence ventricular arr
mias For instance the suggestion that
phenylephrine induced suppression of ventr
arrhythmias depends upon the reflexly in
increase in vagal activity is not supported
recent study Indeed Weiss and colleag
using atrial pacing have shown that the
rhythmic effect of phenylephrine is mostly d
the attendant slowing in heart rate

In the next paragraphs sympathetic and
arrhythmogenic influences will be reviewed
occurring in the following conditions (1) ps
logic stress (2) exercise and (3) sleep The
QT syndrome will then be considered as a p
liar condition in which neural mechanism
lead to lethal arrhythmias

1 Psychologic stress The relationship
tween psychological factors cardiac arrhyth
and sudden death has been dealt with in
reviews we will only discuss here the evid
that the critical link for this relationship
sented by the sympathetic nervous system

There is abundant clinical literature of
anecdotal type showing the occurrence of ca
arrhythmias and even sudden death duri
tionally important events However the
evidence comes as is often the case from ex
mental studies

Verrier Lown and their associates have
the effect of a psychologically stressful e

cervical segment to the fifth thoracic segment was capable of reducing the number of ectopic beats associated with short lasting coronary occlusion[25]

From a clinical point of view it is important to mention the high incidence of ventricular tachyarrhythmias in patients with anterior myo cardial infarctions as was shown by Pantridge s group[9, 6]

b Increased efferent vagal activity As was first shown by Pantridge s group soon after infe rior myocardial infarction there is a very high incidence of bradycardia or hypotension or both which often seems to act as a prelude to ven tricular fibrillation Likewise during transient episodes with electrocardiographic signs of myo cardial ischemia accompanied by pain or not hypotension and bradycardia can occur or hypo tension alone can occur without the tachycardia expected from baroreflex deactivation[13]

The laboratory notion of vagally mediated depressor reflexes from the heart is an old one deriving from the experiments with veratrum alkaloids of von Bezold and Hirt It was not until a hundred years later however that depres sor reflexes with vagal afferent fibers were studied adequately with respect to their possible patho physiological role during experimental coronary occlusion[3, 4] distension of cardiac chambers and increase in coronary pressure

These depressor reflexes act through the excita tion of the vagal and the inhibition of the sympa thetic outflow However what appears as a dan gerous clinical reality does not easily fit in the simple scheme provided by some laboratory find ings indicating that an increased vagal activity reaching the heart especially if associated with a reduction of sympathetic tone should increase electrical stability and raise the fibrillation threshold[3] However the antiarrhythmic effects of the vagus may be augmented or reversed by its profound influence on heart rate in the setting of acute myocardial ischemia[3]

c The sympatho vagal interaction Adminis tration of atropine for management of bradycar dia has been reported to often unmask a simulta neous sympathetic overactivity This is indeed not surprising The left ventricle has a rich senso ry innervation with afferent fibers running both in the vagi and in the sympathetic nerves A mechanical abnormal event with or without the sensitizing contribution of chemical substances has the potentiality of eliciting the following set of reflexes sympatho sympathetic sympatho vagal vago vagal and vago sympathetic Which of these reflexes will prevail will depend on the type of sensory endings excited on the specific nature and location of the abnormal stimulus and on the complex integrating connections in the brain

Yet a frequent pathophysiologic event could be that of an increased vagal *and* sympathetic efferent activity as the result of prevailing vago vagal and sympatho sympathetic reflexes Such a common event would weaken the old conception of vagal and sympathetic outflows working in a sort of reciprocal arrangement Bergamaschi[3] has recently shown that after ligation of the anterior descending coronary artery the simultaneous stimulation of cardiac vagal and sympathetic efferent fibers produced a greater incidence of severe arrhythmias including ventricular fibrilla tion than the separate stimulation of either efferent system

2 Neural mechanisms in arrhythmias not associated with myocardial ischemia

There is a definite experimental proof that sympathetic and vagal activities can also elicit arrhythmias in the absence of any demonstrable degree of myocardial ischemia The sympathetic and vagal arrhythmogenic effects have been stud ied primarily by stimulating or interrupting the neural paths to the heart or by injecting various drugs that interfere with autonomic activity

Electrical stimulation of various areas of the brain has resulted in a diversity of cardiac arrhythmias[33, 4] mostly mediated by activation of the sympathetic nervous system Manning and Cotten showed that the simultaneous increase in both sympathetic and vagal activity was par ticularly detrimental These arrhythmias occur during stimulation and after cessation of the stimulation Evans and Gillis[36] have concluded that arrhythmias produced during the stimula tion are predominantly mediated by the sympa thetic nerves while the others are primarily dependent upon a vagal reflex discharge Ar rhythmias and electrocardiographic changes in duced by brain stimulation may represent an interesting model for arrhythmias and repolariza tion abnormalities often accompanying cerebro vascular accidents.[7, 3]

Relevant to the problem of life threatening

ischemic myocardium may precipitate arrhythmias In particular the rebound of REM sleep which occurs as a consequence of REM sleep deprivation or after withdrawal of drugs such as barbiturates may be quite arrhythmogenic in an ischemic heart[7]

On the other hand there is evidence that quiet sleep may represent a state of even greater risk. During quiet sleep the QT interval is prolonged as compared to REM sleep[73 74] vulnerability to arrhythmias in hypoxic kittens increases[75] and ventricular fibrillation is more rapidly induced by acute ischemia in pigs[76] Skinner and co workers[76] have also shown that pigs with an acute myocardial infarction have more cardiac arrhythmias during sleep as compared to their awake state

Another important clinical condition (8 000 to 10 000 victims per year in the U S) in which lethal cardiac arrhythmias may occur during sleep is the Sudden Infant Death Syndrome The typical clinical story is that of a healthy infant age two to four months put to sleep for a nap or for the night and found dead shortly thereafter or the next morning Although the cause or more probably the causes of these sudden deaths have not been clarified the possibility has recently been proposed that at least some cases of Sudden Infant Death Syndrome might depend upon an abrupt sympathetic discharge taking place through an asymmetrically developed sympathetic innervation of the heart with dominance of left sided nerves

The long QT syndrome The idiopathic long QT syndrome (LQTS) is characterized by prolongation of the QT interval frequent alternation of the T wave and syncopal episodes due to ventricular fibrillation eventually resulting in the sudden death of most affected individuals [9] Crucial for the understanding of the pathogenetic mechanisms is the clinical observation that the syncopal episodes almost always follow an emotional or a physical stress This tight association between emotions such as fear or anger and ventricular fibrillation undoubtedly contributes to the uniqueness of this clinical entity

A most likely pathogenetic mechanism suggested by clinical and experimental data is a congenital imbal [illegible] between right and left cardiac sympath [illegible] with a left dominance Alternatively [illegible] likely the basic defect may be an unk [illegible] ardiac abnormality decreasing electrical stability and sensiti [illegible] myocardium to sympathetic discharges In [illegible] case, there is no doubt that the ventric [illegible] tachyarrhythmias which lead the LQTS p [illegible] to death depend upon sudden increases in [illegible] thetic activity mostly through the domina [illegible] stellate ganglion

Data regarding the pathogenesis of the l [illegible] syndrome have been gathered mostly by [illegible] lation of the sympathetic nervous system [illegible] experimental animals right stellectomy [illegible] produces a relative dominance of left card [illegible] sympathetic nerves results in (1) prolonga [illegible] the QT interval[47 8] (2) increase in ve [illegible] arrhythmias during myocardial ischemia,[0] ex [illegible] cise [9] and emotion[41 6] (3) lowering of the thr [illegible] old for ventricular fibrillation and (4) [illegible] in ventricular excitability[4] Furthermor [illegible] patients with the long QT syndrome alterna [illegible] the T wave has been elicited by blockade of [illegible] right stellate ganglion[83] and has been supp [illegible] by blocking the left stellate ganglion[4] [illegible] tion of the T wave and ventricular arrhythm [illegible] have been produced in animals [9] and in ma [illegible] stimulation of the left stellate ganglion.

The understanding of the mechanisms [illegible] ing ventricular fibrillation has dictated a [illegible] therapeutic approach to the long QT synd [illegible] beta adrenergic blocking agents or left stel [illegible] my The most recent evaluation of the effe [illegible] therapy in the long QT syndrome [1] indicates th [illegible] in over 500 patients beta blockers reduce [illegible] mortality rate from 78% (untreated patie [illegible] 6% At the present time left stellectomy [illegible] the first time in 1970 by Moss and McD [illegible] has been performed in 20 patients all refract [illegible] beta blockers resulting in the suppression [illegible] complete or almost complete of the sy [illegible] attacks With other therapies the mortali [illegible] is still around 50% The available data [illegible] that the first choice treatment is repre [illegible] beta blockers at full dose should howev [illegible] syncopal attacks continue left [illegible] becomes mandatory

3 Therapeutic implications

Attempts to reduce the incidence of li [illegible] ening arrhythmias in patients at high r [illegible] sudden cardiac death should be directed [illegible] those factors which may induce or increase [illegible] diac electrical instability The overwhel [illegible]

ment Dogs were exposed to two different environments a cage in which the animals were left undisturbed and a sling in which they received a transthoracic shock for three consecutive days On days 4 and 5 the effects of the two environments were compared, as the dogs entered the sling they became restless exhibited somatic tremor and their heart rate increased markedly Under this condition it was found that the threshold for repetitive extrasystoles which was considered as a marker of cardiac vulnerability was reduced by 50% That this increase in vulnerabil was mediated by the sympathetic nervous system was indicated by the fact that it was completely prevented by a beta adrenergic blocking drug[58] Furthermore when dogs with a recent myocardial infarction and free of arrhythmias were reexposed to the aversive environment ventricular arrhythmias including ventricular tachycardia occurred these phenomena disappeared when the animals were returned to the quiet

Another hint as to the arrhythmogenic role of stress comes from the observation[60] that farm pigs sufficiently adapted to the laboratory are less prone to ventricular fibrillation after coronary occlusion In this case however beta blockade with propranolol did not afford any protection The possibility has been raised [1] that in this study blockade of beta adrenergic cardiac innervation was inadequate

2 Exercise Exercise can increase the incidence of ventricular arrhythmias not only in patients with coronary heart disease but also in normal subjects[6] Most of these arrhythmias occur in the post exercise recovery period

It is common knowledge that during exercise there are a simultaneous increase in sympathetic tivity and a withdrawal of vagal tone upon cessation of exercise vagal activity immediately resumes while the cardiac effects of catecholamines are still present

Three recent studies have provided evidence on the relationship between the sympathetic nervous system and exercise induced cardiac arrhythmias In dogs performing submaximal exercise on a treadmill some arrhythmias occurred in a small percentage of intact animals and in an equally percentage of animals with left stellectomy arrhythmias were absent after bilateral stellectomy However they were markedly increased after right stellectomy with the left stellate ganglion intact [9] In another study in dogs whose hearts were completely denervated with the exception of the ventrolateral cardiac nerve which originates from the left stellate ganglion arrhythmias were often produced by exercise [3] Likewise in 75 patients who had undergone unilateral or bilateral stellectomy as a treatment of Raynaud s syndrome and who were studied with submaximal exercise on a treadmill [4] exercise induced ventricular arrhythmias appeared in a very small percentage of control subjects with intact stellate ganglia and in patients with left stellectomy These arrhythmias were entirely absent in patients who had a bilateral stellectomy and occurred in a considerable proportion of patients with right stellectomy These studies have shown the important role of cardiac sympathetic nerves in the genesis of arrhythmias during exercise and have indicated the particular arrhythmogenic potential of left sided sympathetic nerves especially when a condition of sympathetic imbalance is created

Another mechanism potentially relevant for the development of arrhythmias during exercise in patients with coronary heart disease is represented by the fact that during exercise coronary flow is still restricted by sympathetic vasoconstrictor tone and that this tonic vasoconstriction is dependent upon nerve fibers passing through the left stellate ganglion Indeed after left stellectomy coronary flow during exercise is higher compared to control condition suggesting that the sympathetic activity may limit the vasodilation of the coronary bed secondary to increased metabolic demands

3 Sleep The effect of sleep on cardiac arrhythmias is still controversial Clinical findings ranged from a complete abolition or an amelioration of cardiac arrhythmias during sleep [5] to an exclusive occurrence of arrhythmias during sleep [6]

REM sleep because of its association with bursts of autonomic activity [6] has been considered for a while the stage of sleep in which the heart is most vulnerable Transient elevations in blood pressure and heart rate occur during REM sleep[69, 70] suggesting that sympathetic bursts may be superimposed on the tonic decrease in sympathetic activity [0, 11] These changes may decrease the electrical stability of the heart and in an

ischemic myocardium may precipitate arrhythmias In particular, the rebound of REM sleep which occurs as a consequence of REM sleep deprivation or after withdrawal of drugs such as barbiturates may be quite arrhythmogenic in an ischemic heart [72]

On the other hand there is evidence that quiet sleep may represent a state of even greater risk During quiet sleep the QT interval is prolonged as compared to REM sleep [73,74] vulnerability to arrhythmias in hypoxic kittens increases [75] and ventricular fibrillation is more rapidly induced by acute ischemia in pigs [76] Skinner and co workers [76] have also shown that pigs with an acute myocardial infarction have more cardiac arrhythmias during sleep as compared to their awake state

Another important clinical condition (8,000 to 10 000 victims per year in the U S) in which lethal cardiac arrhythmias may occur during sleep is the Sudden Infant Death Syndrome The typical clinical story is that of a healthy infant age two to four months put to sleep for a nap or for the night and found dead shortly thereafter or the next morning Although the cause or more probably the causes of these sudden deaths have not been clarified the possibility has recently been proposed that at least some cases of Sudden Infant Death Syndrome might depend upon an abrupt sympathetic discharge taking place through an asymmetrically developed sympathetic innervation of the heart with dominance of left sided nerves

The long QT syndrome The idiopathic long QT syndrome (LQTS) is characterized by prolongation of the QT interval frequent alternation of the T wave and syncopal episodes due to ventricular fibrillation eventually resulting in the sudden death of most affected individuals [78] Crucial for the understanding of the pathogenetic mechanisms is the clinical observation that the syncopal episodes almost always follow an emotional or a physical stress This tight association between emotions such as fear or anger and ventricular fibrillation undoubtedly contributes to the uniqueness of this clinical entity

A most likely pathogenetic mechanism suggested by clinical and experimental data [81] is a congenital imbalance between right and left cardiac sympathetic nerves with a left dominance Alternatively though less likely the basic defect may be an unknown intracardiac abnormality decreasing electrical stability and sensitizing myocardium to sympathetic discharges. In any case there is no doubt that the ventricular tachyarrhythmias which lead the LQTS patients to death depend upon sudden increases in sympathetic activity mostly through the dominant stellate ganglion

Data regarding the pathogenesis of the long QT syndrome have been gathered mostly by manipulation of the sympathetic nervous system. In experimental animals right stellectomy which produces a relative dominance of left cardiac sympathetic nerves results in (1) prolongation of the QT interval [47,82] (2) increase in ventricular arrhythmias during myocardial ischemia [4] exercise [49] and emotion [47,64], (3) lowering of the threshold for ventricular fibrillation [4] and (4) increase in ventricular excitability [4] Furthermore patients with the long QT syndrome alternation of the T wave has been elicited by blockade of the right stellate ganglion [3] and has been suppressed by blocking the left stellate ganglion Alternation of the T wave and ventricular arrhythmias have been produced in animals and in man by stimulation of the left stellate ganglion

The understanding of the mechanisms triggering ventricular fibrillation has dictated a logical therapeutic approach to the long QT syndrome beta adrenergic blocking agents or left stellectomy The most recent evaluation of the effect of therapy in the long QT syndrome indicates that in over 500 patients beta blockers reduce the mortality rate from 78% (untreated patients) to 6% At the present time left stellectomy used for the first time in 1970 by Moss and McDonald has been performed in 20 patients all refractory to beta blockers resulting in the suppression or the complete or almost complete of the syncopal attacks With other therapies the mortality rate is still around 50% The available data indicate that the first choice treatment is represented by beta blockers at full dose should however syncopal attacks continue left stellectomy becomes mandatory

3 Therapeutic implications

Attempts to reduce the incidence of life-threatening arrhythmias in patients at high risk of sudden cardiac death should be directed against those factors which may induce or increase cardiac electrical instability The overwhelming

dence pointing to the crucial role of the cardiac innervation as the precipitating factor implies that measures which prevent or antagonize sympathetic or parasympathetic effects might prove beneficial

Beta adrenergic blocking drugs have gained wide clinical acceptance as antiarrhythmic agents Along the same line of thought surgical ablation of the cardiac sympathetics has recently been suggested as a possible therapeutic procedure Both approaches will be briefly reviewed Finally the possibility will be considered of pharmacological blockade of parasympathetic efferent activity

1 Beta adrenergic blocking agents That beta adrenergic blocking agents may be effective in treating or preventing life threatening arrhythmias in coronary patients is suggested by animal experiments which show that these agents seem to reduce the number of ventricular dysrhythmias resulting from coronary occlusion [6]

The effectiveness of these compounds in clinical dysrhythmias is incompletely documented however Taggart and colleagues [7] by monitoring the electrocardiogram for prolonged time in subjects performing their daily tasks have observed that beta blockade is highly effective in protecting against emotionally induced arrhythmias in both normal subjects and in patients with coronary heart disease Yet the clinical condition in which prompt administration of beta adrenergic antagonists may in principle be most advantageous acute myocardial infarction with disrhythmias generally requires urgent therapeutic measures thus precluding studies which satisfy the stringent rules of clinical trials The majority of investigators [8, 9] who have tried intravenous administration of various beta blockers in patients with acute myocardial infarction have found that no more than 50% of patients treated responded favorably the drugs being most effective in sinus tachycardia and ventricular premature beats and least effective for reversing atrial fibrillation It is worth emphasizing furthermore that the benefit risk balance of administrating a beta blocker to patients under such as dangerous condition as acute myocardial infarction is always difficult to predict and to assess the outcome in the individual case will largely depend on the net balance between further depression of sympathetic dependent cardiac contractility on one side and an improvement in pumping function and decreased risk of ventricular fibrillation by reversion of tachyarrhythmias on the other side

It should also be considered in view of the evidence summarized previously suggesting that dysrhythmias in early myocardial infarction may be mediated by either the cardiac sympathetics or the vagi according to the infarction site (anterior versus inferior) that more definite advantages may be obtained by limitating the use of beta blockade to patients with anterior myocardial infarction

A further application of beta blockers which lends itself to a better though extremely laborious testing is in preventing sudden death and the recurrence of cardiac events when given over the long term following myocardial infarction A few trials recently completed [90] have shown favorable results of the long term administration of the beta adrenergic blocking agents alprenolol and practolol The practolol study[59, 90] indicated that the protective effect of the drug consisting in a significant reduction of over all mortality rate and in sudden death was most consistent in those patients whose original infarcts were localized anteriorly again a clear reference to Pantridge s work Because of the severe side effects of practolol continuation of its favorable results is being sought in other trials presently under way and by using other beta blockers

The striking favorable effects of beta blocking therapy in preventing lethal arrhythmias in the long QT syndrome[79, 81] have already been summarized in the preceding section

2 Left sympathectomy An alternative procedure for preventing or limiting sympathetic arrhythmogenic influences upon the heart is represented by cardiac sympathectomy Evidence from animal experiments that we have summarized above clearly shows that the following beneficial results can be obtained even when cardiac sympathectomy is limited to the left side and only consists in left stellectomy Indeed left stellectomy reduces the incidence of ventricular arrhythmias associated with short lasting coronary occlusion it produces a marked increase in the threshold for ventricular fibrillation it prolongs the ventricular refractory period [6] it increases the capability of the coronary bed to dilate it does not reduce cardiac performance during exer

Schwartz, A M. Brown, A. Malliani, and A. Zanchetti, Eds., New York, 1978 Raven Press, p 139

33 Korteweg G C J., Boeles, J Th. F and Ten Cate J Influence of stimulation of some subcortical areas on the electrocardiogram J Neurophysiol. 20 100 1957

34 Melville, K. I., Blum B., Shister H E., and Silver M D Cardiac ischemic changes and arrhythmias induced by hypothalamic stimulation Am. J Cardiol. 12 781 1963

35 Manning J W., De V Cotten, M Mechanism of cardiac arrhythmias induced by diencephalic stimulation Am J Physiol 203 1120 1962.

36 Evans, D E and Gillis, R A. Reflex mechanisms involved in cardiac arrhythmias induced by hypothalamic stimulation, Am J Physiol. 234 H199 1978

37 Burch, G E., Meyers, R., and Abildskov J A. A new electrocardiographic pattern observed in cerebrovascular accidents, Circulation 9 719 1954

38 Abildskov J A. Central nervous system influence upon electrocardiographic waveforms, *in* Advances in Electrocardiography R. C Schlant and J W Hurst Eds. New York 1972, Grune & Stratton Inc. p 423

39 Satinsky J., Kosowsky B., Lown B and Kerzner J Ventricular fibrillation induced by hypothalamic stimulation during coronary occlusion, Circulation 44 60 1971

40 Verrier R. L., Calvert A., and Lown B Effect of posterior hypothalamic stimulation on the ventricular fibrillation threshold Am. J Physiol. 228 923 1975

41 Verrier R L., Thompson P., and Lown, B Ventricular vulnerability during sympathetic stimulation role of heart rate and blood pressure, Cardiovasc. Res. 8 602, 1974

42. Hageman G R. Goldberg J M Armour J A., and Randall, W C Cardiac dysrhythmias induced by autonomic nerve stimulation, Am J Cardiol. 32 823 1973

43 Kliks, B R., Burgess, M J., and Abildskov J A. Influence of sympathetic tone on ventricular fibrillation threshold during experimental coronary occlusion Am. J Cardiol. 36 45 1975

44 Schwartz, P J Snebold N G., and Brown, A. M Effects of unilateral cardiac sympathetic denervation on the ventricular fibrillation threshold, Am J Cardiol. 37 1034 1976

45 Schwartz, P J., Stone H L., and Brown, A. M. Effects of unilateral stellate ganglion blockade on the arrhythmias associated with coronary occlusion Am Heart J 92 589 1976

46 Schwartz, P J., Verrier R. L., and Lown, B Effect of stellectomy and vagotomy on ventricular refractoriness, Circ Res. 40 536 1977

47 Schwartz, P J Experimental reproduction of the long Q-T syndrome Am. J Cardiol. 41 374 1978.

48 Austoni, P., Rosati R., Gregorini, L., Bianchi, E., Bortolani, E., and Schwartz, P J Stellectomy and exercise in man Am. J Cardiol. 43 399 1979

49 Schwartz, P J and Stone H L. Effects of unilateral stellectomy upon cardiac performance during exercise in dogs, Circ Res. 44 637 1979

50 Lown B., and Verrier R. L. Neural activity and ventricular fibrillation N Engl J Med 294 1165 1976.

51 Verrier R. L. and Lown B Sympathetic parasympathetic interactions and ventricular electrical stability *in* Neural Mechanisms in Cardiac Arrhythmias, P J Schwartz, A. M Brown A. Malliani, and A Zanchetti, Eds., New York, 1978, Raven Press, p 75

52. Kent, K. M., Epstein S E Cooper T., and Jacobowitz, D M Cholinergic innervation of the canine and human ventricular conducting system. Autonomic and electrophysiological correlation Circulation 50 948 1974

53 Watanabe A. M., and Besch, H. R., Jr [illegible] between cyclic adenosine monophosphate and cyclic guanosine monophosphate in guinea pig ventricular myocardium Circ. Res. 37 309 1975.

54. Waxman M B., and Wald, R. W Termination of ventricular tachycardia by increase in cardiac vagal drive Circulation 56 385 1977

55 Weiss T., Mancia, G Del Bo A Cavoretto, D [illegible] S. Preti, L., and Schwartz P J The role of [illegible] in the phenylephrine induced suppression of premature ventricular beats Europ J Clin. Invest 9 [illegible] 1979

56 Zanchetti, A., and Malliani, A Neural and psychological factors in coronary disease Acta Cardiol. [illegible] (Suppl 20) 69 1974

57 Lynch, J J., Paskewitz, D A., Gimbel, K. S and Thomas, S A. Psychological aspects of cardiac arrhythmias, Am Heart J 93 645 1977

58 Matta R J., Lawler J E and Lown B. [illegible] instability in the conscious dog effects of psychologic stress and beta adrenergic blockade Am. J Cardiol. 38 594 1976.

59 Corbalan R., Verrier R. L., and Lown, B. Psychological stress and ventricular arrhythmias during myocardial infarction in the conscious dog. Am. J Cardiol. 34 692, 1974

60 Skinner J E., Lie J T., and Entman, M L. [illegible] tion of ventricular fibrillation latency following coronary artery occlusion in the conscious pig. Circulation 51 656 1975

61 Lown, B., Verrier R. L., and Rabinowitz, S. H. Neural and psychologic mechanisms and the problem of sudden cardiac death Am. J Cardiol. 39 890 1977

62. Jelinek, M V., and Lown, B Exercise stress testing for exposure of cardiac arrhythmia. Progr Cardiovasc Dis 16 497 1974

63. Randall, W C Thomas, J X., E [illegible] D E., and Rozanski, G J Cardiac dysrhythmias associated with autonomic nervous system imbalance in the conscious dog *in* Neural Mechanisms In Cardiac Arrhythmias, P J Schwartz, A. M Brown, A. Malliani, and A. Zanchetti, Eds., New York, 1978, Raven Press, p. 123

64 Schwartz, P J., and Stone H L. Unilateral [illegible] my and sudden death, *in* Neural Mechanisms in Cardiac Arrhythmias, P J Schwartz, A. M. Brown, A. Malliani, and A. Zanchetti, Eds., New York, [illegible] Raven Press, p 107

65 Shahaway M., Arrhythmias and the varieties of [illegible] N Engl. J Med 282 815 1970

66 Lown B Tykocinski, M Garfein A., and [illegible] Sleep and ventricular premature beats, Circulation 48 691 1973

67 Nevins, D B First and second degree A V heart block with rapid eye movement sleep Ann. [illegible] 76 981 1972

68 Rosenblatt G., Hartmann E., and Zwilling G R. Cardiac irritability during sleep and dreaming J Psychosomatic Res. 17 129 1973.

69 Guazzi, M., Mancia G Kumazawa, T Baccelli, G and Zanchetti, A. Effects of cardiac denervation on blood pressure and heart rate during natural sleep in the cat Cardiovasc Res. 2 265 1968.

70 Baccelli, G., Albertini, R., Mancia G and Zanchetti A. Central and reflex regulation of sympathetic vasoconstrictor activity to limb muscles during desynchronized sleep in the cat. Circ Res. 35 625, 1974

71 Baust, W., Weidinger H., and Kirchner F [illegible]

influences an approach that has been neglected for years perhaps as a consequence of the dominant role played by the so called pump physiology in the traditional approach to cardiovascular disease

This new approach is already reflected in useful therapeutic measures to correct life threatening arrhythmias both in frequently occurring cases of cardiac ischemia and in the rarer conditions in which ischemia is absent it represents the rationale of current promising attempts to provide prevention of myocardial infarction and sudden death Hopefully it will stimulate further research which may lead to more sophisticated and improved therapeutic strategies in the near future

REFERENCES

1 Cranefield P F Wit A L and Hoffman B F Genesis of cardiac arrhythmias Circulation 47 190 1973
2 Han J and Goel B G Electrophysiology precursors of ventricular tachyarrhythmias Arch Intern Med 129 749 1972
3 Cranefield P F The conduction of the cardiac impulse Mount Kisco New York 1975 Futura Publishing Company
4 Danielopolu D Etat actuel du traitement chirurgical de l angine de poitrine Cardiologia 14 45 1949
5 Jonnesco T Traitement chirurgical de l angine de poitrine par la résection du sympathique cervico thoracique Presse Méd 29 193 1921
6 Leriche R Herman L and Fontaine R Ligature de la coronaire gauche et function du coeur après énervation sympathique C R Soc Biol 107 547 1931
7 Cox W V and Robertson H F The effect of stellate ganglionectomy on the cardiac function of intact dogs and its effect on the extent of myocardial infarction and on cardiac function following coronary artery occlusion Am Heart J 12 285 1936
8 Corr P B and Gillis R A Autonomic neural influences on the dysrhythmias resulting from myocardial infarction Circ Res 43 1 1978
9 Webb S W Adgey A A J and Pantridge J F Autonomic disturbance at onset of acute myocardial infarction Br Med J 3 89 1972
10 Pantridge, J F Autonomic disturbance at the onset of acute myocardial infarction *in* Neural Mechanisms in Cardiac Arrhythmias P J Schwartz A M Brown A Malliani, and A Zanchetti, eds New York 1978 Raven Press p 7
11 Littler W A Honour J Sleight P and Stott F D Direct arterial pressure and electrocardiogram in unrestricted patients with angina pectoris Circulation 48 125 1973
12 Roughgarden J W and Newman E V Circulatory changes during the pain of angina pectoris Am J Med 41 935 1966
13 Maseri, A, Severi, S De Nes, M L Abbate A Chierchia S Marzilli, M Ballestra A M Parodi O Biagini, A and Distante A Variant angina One aspect of a continuous spectrum of vasospastic myocardial ischemia Am J Cardiol 42 1019 1978
14 Malliani, A Schwartz P J and Zanchetti, A A sympathetic reflex elicited by experimental coronary occlusion Am J Physiol 217 703 1969
15 Brown A M and Malliani, A Spinal sympathetic reflexes initiated by coronary receptors, J Physiol 212 685 1971
16 Malliani A and Lombardi F Neural reflexes associated with myocardial ischemia *in* Neural Mechanisms in Cardiac Arrhythmias P J Schwartz A M Brown A Malliani, and A Zanchetti eds New York 1978 Raven Press, p 209
17 Schwartz P J Pagani, M Lombardi, F, Malliani, A and Brown A M A cardiocardiac sympathovagal reflex in the cat Circ Res 32 215 1973
18 Malliani A Recordati G and Schwartz P J Nervous activity of afferent cardiac sympathetic fibres with atrial and ventricular endings, J Physiol 229 457 1973
19 Casati R Lombardi, F and Malliani A Afferent sympathetic unmyelinated fibres with left ventricular endings in cats J Physiol 292 135 1979
20 Lombardi F Della Bella P Casati R and Malliani A Effects of intracoronary administration of bradykinin on the impulse activity of afferent sympathetic unmyelinated fibers with left ventricular endings in the cat Circ Res. (In press)
21 Malliani A Peterson D F Bishop V S and Brown A M Spinal sympathetic cardiocardiac reflexes Circ Res 30 158 1972
22 von Bezold A and Hirt L Uber die physiologischen Wirkungen des essigsauren Veratrins Untersuch Physiol Lab Wurzbur 1 73 1867
23 Costantin L R Extracardiac factors contributing to hypotension during coronary occlusion Am J Cardiol 21 205 1963
24 Thoren P Vagal reflexes elicited by left ventricular C fibers during myocardial ischemia in cats *In* Neural Mechanisms in Cardiac Arrhythmias, P J Schwartz A M Brown A Malliani and A Zanchetti (Eds) New York 1978 Raven Press p 179
25 Schwartz P J Foreman R D, Stone H L and Brown A M Effect of dorsal root section on the arrhythmias associated with coronary occlusion Am J Physiol 231 923 1976
26 Guazzi, M Polese A, Fiorentini, C Magrini, F, and Bartorelli C Left ventricular performance and related haemodynamic changes in Prinzmetal s variant angina pectoris Br Heart J 33 84 1971
27 Aviado D M and Schmidt C F Reflexes from stretch receptors in blood vessels heart and lungs Physiol Rev 35 247 1955
28 Brown A M The depressor reflex arising from the left coronary artery of the cat J Physiol 184 825 1966
29 Kolman B Verrier R L and Lown B The effect of vagus nerve stimulation upon vulnerability during coronary artery occlusion and reperfusion Circulation 52 578 1975
30 Kent K M and Epstein S E Neural basis for the genesis and control of arrhythmias associated with myocardial infarction Cardiology 61 61 1976
31 Verrier R L and Lown B Influence of neural activity on ventricular electrical stability during acute myocardial ischemia and infarction *in* Management of ventricular tachycardia—role of mexiletine Oxford —Amsterdam 1978 Excerpta Medica p 133
32 Bergamaschi, M Role of the sympathetic and parasympathetic innervation in the genesis of ventricular arrhythmias during experimental myocardial ischemia *in* Neural Mechanisms in Cardiac Arrhythmias P J

Clinical pathologic conference

Perioperative hypertensive crisis and hemorrhagic diathesis Fatal complication of clinically unsuspected pheochromocytoma

J T Lie M D
Byron A Olney M D
John A Spittell M D
Rochester Minn

Case presentation

Dr Olney The patient a 77 year old woman was first seen at the Mayo Clinic on November 30 1977 with a six month illness characterized chiefly by malaise fatigue anorexia weight loss and fever Her previous medical history included central retinal vein occlusion in 1976 hypertension of ten years duration a heart murmur known for 20+ years and hysterectomy oophorectomy in 1956 She was currently taking Dyazide one capsule per day for her hypertension

During the preceding six months she had consulted several local physicians and was given a variety of tentative diagnoses for her illness including upper respiratory infection pneumonia pulmonary edema and urinary infection Documentation of these diagnoses was lacking and therapies directed at the conditions failed to appreciably alter her apparently deteriorating well being The physical findings described at various times during this period included blood pressure recording ranging from 110/70 to 190/80 mm Hg and a grade 2/6 systolic ejection murmur Some of the laboratory test results were a white blood cell count of 16 200/cu mm sedimentation rate 40 mm/hr Westergren blood glucose 150 to 212 mg/dl normal urinalyses and normal chest roentgenogram

On November 30 1977, she w to

Rochester Methodist Hospital By this time she was recorded as having had a 20 kilogram weight loss She suffered from a constant cough with some production of dark brown sputum Additional history included five or six "spells" over the preceding three months characterized by vertigo and tachycardia of 10 to 15 minutes duration followed by somnolence for 4 to 5 hours There was some question of loss of consciousness at these times but this was not certain

On physical examination her blood pressure was 125/65 mm Hg and her body temperature was 37 2° C on admission She had a fine tremor of the hands and tongue Her lungs were clear to auscultation The apex impulse was palpable 1 cm lateral to the midclavicular line with a parasternal lift described A grade 3/6 systolic murmur was present at the base of the heart, with radiation to the carotid arteries and the apex This was considered to be a left ventricular outflow murmur Neither gallop rhythm nor diastolic murmur were auscultable

On the evening of the first hospital day her temperature rose to 39 4 C Blood cultures drawn on this day were later reported to be positive for a gram positive coccus A total of nine blood cultures were drawn during her first two h days and they were all positive for the sa nism which was further identified as

bovis

ts of the initial evaluation included f 11 5 g/dl white blood cell co with 72% neutrophils and telet count of 151 000/cu mm 10 6 second serum sodium potassium 4 3 mEq/L

From the Department of Pathology and Cardiovascular Diseases, Departm nt of Clin c and Mayo Fou 1 t on Rochest
Recei ed for publ at F 1 4 1 80
Reprint requests J 1 M D Depa Anatomy Mayo Cli 1 st r M nn 5

0 © 1980 The C V Mosby Co

ic activity during natural sleep and arousal Arch Ital Biol. 160 379 1968

72 Orr W C and Shappell S D REM sleep and cardiac arrhythmias Circulation 52 519 1975

73 Haddad G G Epstein M A F Epstein R A Mazza N M., Mellins R B and Krongrad E The QT interval in aborted SIDS infant. Ped Res 13 136 1978

74. Steinschneider A Sudden infant death syndrome and prolongation of the Q T interval Am J Dis. Child 132 688 1978

75 Baker T L and McGinty D J Reversal of cardiopulmonary failure during active sleep in hypoxic kittens implication for sudden infant death Science 198 419 1977

76 Skinner J E Mohr D N and Kellaway P Sleep-stage regulation of ventricular arrhythmias in the unanesthetized pig Circ Res. 37 342 1975

77 Schwartz P J Cardiac sympathetic innervation and the Sudden Infant Death Syndrome A possible pathogenetic link Am J Med 60 167 1976

78 Schwartz P J The Sudden Infant Death Syndrome *in* Reviews in Perinatal Medicine E M Scarpelli and E V Cosmi, Eds New York Raven Press (In press 1980)

79 Schwartz P J Periti M and Malliani, A The long Q T syndrome AM HEART J 89 378 1975

80 Moss, A J and Schwartz P J Sudden death and the idiopathic long Q T syndrome Am J Med 66 6 1979

81 Schwartz P J The long Q T syndrome *in* Sudden Death H J J Wellens, and H E Kulbertus (Eds) The Hague 1980 M Nijhoff p 358

82 Yanowitz, R., Preston J B and Abildskov J A Functional distribution of right and left stellate innervation of the ventricles production of neurogenic electrocardiographic changes by unilateral alteration of sympathetic tone Circ Res. 18 416 1966

83 Moss A J., and McDonald J Unilateral cervicothoracic sympathetic ganglionectomy for the treatment of long Q T interval syndrome N Engl. J Med 285 903 1971

84 Crampton R Preeminence of the left stellate ganglion *in the long Q T syndrome Circulation 59 769 1979*

85 Schwartz P J and Malliani, A Electrical alternation of the T wave Clinical and experimental evidence of its relationship with the sympathetic nervous system and with the long Q T syndrome AM HEART J 89 45 1975

86 Khan, M I Hamilton J T and Manning G W Early arrhythmias following experimental coronary occlusion in conscious dogs and their modification by beta adrenoceptor blocking drugs, AM HEART J 86 347 1973

87 Taggart P., Carruthers M and Somerville W Electrocardiogram plasma catecholamines and lipids, and their modification by oxprenolol when speaking before an audience Lancet 2 341 1973

88 Sloman G Robinson J S., and McLean K Propranolol (Inderal) in persistent ventricular fibrillation Br Med J 1 895 1965

89 Lemberg L., Castellanos A. and Arcebal, A G.. The use of propranolol in arrhythmias complicating acute myocardial infarction AM HEART J 80 479 1970

90 Kreus K. E., Salokannel, S J., Isomaki, H., and Warıs E K Alprenolol in the treatment of arrhythmias in acute coronary patients Acta Med Scand 188 375 1970

91 Sandler G and Pistevos A C Use of oxprenolol in cardiac arrhythmias associated with acute myocardial infarction Br Med J 1 254 1971

92 Jewitt D E and Croxson R Practolol in the management of cardiac dysrhythmias following myocardial infarction and cardiac surgery Postgrad Med J (Suppl 47) 25 1971

93 Lemberg L Arcebal A G Castellanos A Jr and Slavin D Use of alprenolol in acute cardiac arrhythmias, Am J Cardiol 30 77 1972

94 Allen J D., Pantridge J F and Shanks R G The effects of practolol on the dysrhythmias complicating acute ischemic heart disease Am J Med. 58 199 1975

95 Biron P Proulx A Lapointe L Nadeau R., and Tremblay G Properties of acebutolol in twenty patients with cardiac arrhythmias, Europ J Clin Pharmacol 8 11 1975

96 Taylor S H., and Burley D M Beta adrenoceptor blocking drugs in post myocardial infarction dysrhythmias, Proc R Soc Med (Suppl 11) 11 1977

97 Vedin A. Wilhelmsson C., and Werko L. Chronic alprenolol treatment of patients with acute myocardial infarction after discharge from hospital Acta Med Scand (Suppl 575) 1 1975

98 Ahlmark G and Saetre H. Long term treatment with beta blockers after myocardial infarction Europ J Clin Pharmacol. 10 77 1976

99 Multicentre International Study Improvement in prognosis of myocardial infarction by long term beta adrenoceptor blockade using practolol, Br Med J 3 735 1975

100 Multicentre International Study Supplementary Report. Reduction in mortality after myocardial infarction with long term beta adrenoceptor blockade Br Med J 2 419 1977

101 *Schwartz P J., and Stone H L. Tonic influence of the* sympathetic nervous system on myocardial reactive hyperemia and on coronary blood flow distribution in dogs Circ Res. 41:51 1977

102 Schwartz P J and Stone H L. Post-denervation supersensitivity and left stellectomy Am J Cardiol. 43:381 1979

103 Schwartz P J., and Stone H L. Left stellectomy in the prevention of ventricular fibrillation due to acute myocardial ischemia in conscious dogs with an anterior myocardial infarction Circulation 62 December 1980

104 Adgey A A J., Geddes, J S., Mulholland H C Keegan D A. J and Pantridge J F Incidence significance and management of early bradyarrhythmia complicating acute myocardial infarction Lancet 2 1097 1968

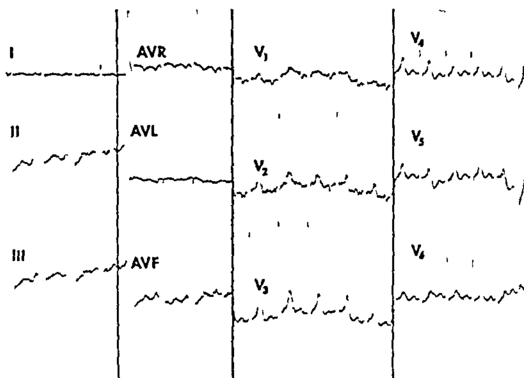


Fig 2 Admission electrocardiogram of November 30 1977 showing sinus tachycardia at the rate of 130 per minute and minor nonspecific ST T wave changes

vegetations on the left coronary and noncoronary valve cusps The aortic valve was replaced with a Bjork Shiley prosthesis At the completion of the surgery bleeding difficulties were encountered with hemodynamic instability Hemostasis was eventually achieved and she was treated with intravenous infusion of sodium nitroprusside because the systolic blood pressure had abruptly risen to 280 mm Hg Following this her systolic blood pressure fell transiently to 60 mm Hg before a more even control was achieved

In the early postoperative hours the patient had further bleeding problems from the surgical site necessitating a reoperation to secure hemostasis Her prothrombin time activated partial thromboplastin time and fibrin split products were now elevated and the plasma fibrinogen was low She was deeply comatose throughout the immediate postoperative period and she died the next day

Clinical discussion

DR SPITTELL To recapitulate what has been outlined in the case presentation the patient was an elderly woman who came here with a six month illness characterized by malaise fatigue anorexia weight loss and fever all fairly nonspecific symptoms She had a past medical history that included hypertension of 10 years duration and a heart murmur for 20 years You will note that prior to being seen here she had been managed as having had pneumonia but full documentation of this diagnosis was lacking Her laboratory studies included a sedimentation rate which was in a never never land of 40 mm/hr I would call your attention to her fasting blood glucose of 150 to 212 mg/dl and her blood pressure which ranged from 110/70 to 190/90 mm Hg in her past workups By the time she arrived here on November 30 she had had a 20 kilogram weight loss in the preceding six months Also noted were a couple of spells characterized by some vertigo and tachycardia followed by somnolence and possibly by loss of consciousness Other physical findings were as recorded and you will note that she had a grade 3/6 systolic murmur

The patient had fever during her initial day of hospitalization The growth of *Streptococcus bovis* from multiple blood cultures is worth spending a few minutes discussing *Streptococcus bovis* is a group D nonenterococcal streptococcus and there was a recent report by Klein and colleagues describing some unusual associations of infections by this particular organism These

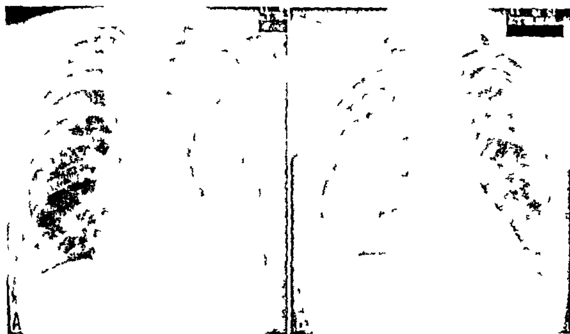


Fig 1 A Admission chest roentgenogram of November 30 19— showing a normal cardiac silhouette and pulmonary vascularity B Preoperative chest roentgenogram of December 15 19— showing increased pulmonary vascular markings and changes consistent with interstitial edema

blood creatinine 1 3 mg /dl fasting blood glucose 105 mg /dl serum glutamic oxaloacetic transaminase 27 U /L (normal 8 to 20 U /L) serum bilirubin 0 6 mg /dl total thyroxine 4 2 μg/100 ml (normal 5 to 13 5 μg/100 ml) syphilic serology nonreactive antinuclear antibody negative and serum iron 33 μg/dl (normal 60 to 180 μg/dl) with total iron binding capacity of 10% saturation (normal 18% to 50%) Serum albumin was slightly increased and gamma globulin was slightly decreased. The fungal and brucella blood cultures acid fast smears sputum cytology and urine cultures were all negative An intermediate tuberculin skin test showed 10 mm of induration An excretory urogram was normal and the admission chest roentgenogram (Fig 1A) showed some scattered fibrosis at the lung base and a normal sized cardiac silhouette An electrocardiogram (Fig 2) showed sinus tachycardia with minimal nonspecific ST T wave changes An ear nose and throat consultation was obtained regarding the vertigo spells and these were diagnosed as benign positional vertigo Two separate echocardiograms were done and were interpreted as negative for valvular vegetations though they did demonstrate evidence of calcium deposits on the aortic valve

After the initial positive blood culture results the patient began receiving intravenous aqueous penicillin G 20 million units every 24 hours plus streptomycin 500 mg every 12 hours. When the organism was further identified as *Streptococcus bovis* the antimicrobial therapy was changed to procaine penicillin 1.2 million units every 6 hours plus streptomycin 500 mg every 12 hours Despite this antibiotic regimen the patient continued to have malaise and a low grade daily fever of approximately 38° C

On the twelfth hospital day a 3/6 diastolic murmur of aortic insufficiency was heard for the first time Because the patient s condition continued to deteriorate aortic valve surgery was contemplated At that time two consecutive blood cultures were negative and the white blood cell count was 6 700/cu mm The prothrombin time activated partial thromboplastin time and the plasma fibrinogen were normal The electrocardiogram was unchanged and the chest roentgenogram (Fig 1B) now showed some interstitial edema The urinalysis showed 3+ red cells and hemoglobin in the supernatant

On December 19 1977 she went to surgery for aortic valve replacement At operation the aortic valve was described as calcified with extensive



Fig 4 *A* Gross appearance of pheochromocytoma attached to the right adrenal gland *(arrows)* *B* Photomicrograph of pheochromocytoma (Hematoxylin and eosin stain original magnification ×160)

murmur Subsequently as you note in the case presentation the patient s condition deteriorated and accordingly, on December 19 she underwent aortic valve replacement The chest roentgenogram (Fig *1B*) of December 15 four days before surgery showed changes of pulmonary venous congestion

At the completion of her surgery she had difficulties both with bleeding and with hemodynamic instability The surgeons eventually achieved hemostasis and managed her labile blood pressure with sodium nitroprusside However despite a second operation the patient never really responded and unfortunately succumbed the next day

We are faced then with a patient who had bacterial endocarditis and her aortic valve replaced perioperative labile hypertension and hemorrhagic diathesis and then was comatose following surgery I think one naturally must consider neurologic complications in this particular context and the paper published by Jones and co workers from this institution on the neurologic complications of bacterial endocarditis is worth summarizing briefly here Of 385 patients reviewed about 15% or 55 had a neurologic complication Of the total number of patients about 3% or 11 patients had a documented cerebral hemorrhage In these 11 cases the hemorrhage was intracerebral in eight and primarily subarachnoid in three The authors concluded that rupture of a mycotic aneurysm was the primary cause for the intracranial hemorrhage in their 11 patients This would mean that if all the people in their series who experienced cerebrovascular hemorrhage had mycotic aneurysms as the cause the incidence of ruptured intracranial mycotic aneurysm in bacterial endocarditis is about 3%

An advantage of having had the opportunity to review the patient s clinic and hospital records was the chance to read each and every note recorded The resident who did the admission workup on this patient made the following observations in his initial note *The patient was hypertensive for nine to 10 years she had had spells of vertigo with tachycardia for three months and she had had orthostatic spells for years* In the very last physician s note in the record at the time the patient died it was recorded that the blood pressure had been swinging widely from 250/160 to 30/0 mm Hg unrelated to any of our measures This to me was a very telling observation

I think that there are three diagnostic considerations in this woman in addition to her having had recent bacterial endocarditis The first is the possibility of an occult colon carcinoma associated with a *Streptococcus bovis* endocarditis The second consideration is rupture of a cerebral

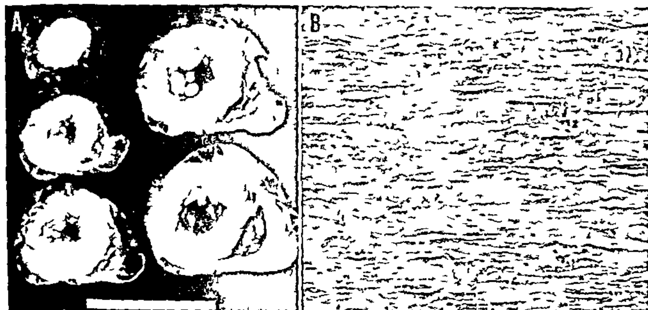


Fig 3 A Gross appearance of five consecutive slices of the transversely sectioned heart showing diffuse epicardial hemorrhage symmetrical left ventricular hypertrophy and absence of any old or recent myocardial infarction B Photomicrograph of subendocardium showing myofibrillar degeneration (Hematoxylin and eosin stain original magnification ×160)

investigators cultured the fecal flora of 278 subjects made up of seven different groups There were 105 control patients 63 patients with carcinoma of the colon 25 with inflammatory bowel disease 37 with other gastrointestinal disorders 12 with histories of previous carcinoma of the colon 15 patients with recently performed barium enemas and 21 patients with a noncolonic neoplasm In some patients cultures were taken from other sites on the body as well None of those samples from the axillary skin or the vagina showed positive cultures and only rarely (three of 45) could the organism be isolated from the throat or gingiva However on their fecal flora studies 56% of the 63 patients with cancer of the colon cultured *Streptococcus bovis* a significantly greater incidence of positive cultures for this particular organism than in any of the other patient groups examined The authors point out further that *Streptococcus bovis* may cause endocarditis almost as frequently as enterococci Although the association of carcinoma of the colon and infective endocarditis has been reported in only nine patients in at least four and possibly six of those nine patients the microorganism responsible for the endocarditis was *Streptococcus bovis* They conclude that it is prudent to evaluate patients with *Streptococcus bovis* endocarditis for possible carcinoma of the colon I think this is a very worthwhile piece of information to be brought to your attention

Proceeding further we see from the laboratory test results that our patient was anemic she had a modestly elevated blood creatinine and her fasting blood glucose was very slightly elevated (105 mg/dl) Her excretory urogram was normal as was her admission chest roentgenogram (Fig 14) Because the patient described episodes of vertigo the ear nose and throat service was asked to see her in consultation and after their examination they concluded that she had benign positional vertigo

The original cardiovascular consultant who saw this woman noted that she had been sick for six months she had a heart murmur she was anemic and she had had fever and weight loss He considered the possibility of bacterial endocarditis but he was concerned because in spite of her having had this illness for six months she did not have an aortic insufficiency murmur Two echocardiograms were done but did not really help in the diagnosis or in the identification of valvular vegetations Nonetheless after the results of the blood cultures were reported a therapeutic antibiotic regimen was instituted Then finally 12 days later the first observer noted a diastolic

made through workups of hypertension in eight patients as an incidental finding at laparotomy for an unrelated condition in four patients and because of the associated endocrinopathy in one patient Of the 41 patients with clinically unsuspected pheochromocytoma death was directly or indirectly related to the tumor and its complications in 30 patients—11 had intraoperative hypertensive or hypotensive crisis 11 had cardiac failure seven had cerebral hemorrhage and one had metastases[6]

Unexpected postanesthetic death and death during surgical procedures for unrelated conditions are well known complications of unsuspected pheochromocytoma[7,8] The surgical procedure may be a simple one such as the incision of an infected finger pulp or a breast biopsy[9] Pheochromocytoma is a true great mimic its clinical manifestations may be kaleidoscopic or minimal[4] Effective biochemical tests for the detection of pheochromocytoma are available[10] However a high index of suspicion is a prerequisite for the clinical diagnosis of pheochromocytoma If diagnosed it is curable in about 90% of patients but will eventually be lethal in almost all cases if untreated[4] Think of it confirm it find it and remove it[11] remains sound advice

REFERENCES

1 Klein R S Recco R A Catalano M T Edberg S C, Casey J I and Steigbigel N H Association of *Streptococcus bovis* with carcinoma of the colon, N Engl J Med 297 800 1977
2 Jones H R, Jr Seikert R G and Geraci J E Neurologic manifestations of bacterial endocarditis Ann Intern Med 71 21 1969
3 Reichenbach D D and Benditt E P, Catecholamines and cardiomyopathy The pathogenesis and potential importance of myofibrillar degeneration Human Pathol 1 125 1970
4 Manger W M, and Gifford R W Jr Pheochromocytoma New York 1977 Springer Verlag, pp 3[illegible]
5 Mayo C H Paroxysmal hypertension with tumor of retroperitoneal nerve J.A.M.A. 89 104[illegible] 19[illegible]
6. Sutton M G St J Lie J T Carney J A, and Sheps S G Clinically unsuspected pheochromocytoma, Circulation 58(Suppl 2) 17 1978
7 Apgar V and Papper E M Pheochromocytoma—anesthetic management during surgical treatment, Arch Surg 62 634 1951
8 Coates I A and Ligal W M Postanaesthetic death from pheochromocytoma without hypertension, Lancet 1 1374 1961
9 Seward E H Death from pheochromocytoma Lancet 2 903 1961
10 Bravo E L Tarazi R C Gifford, R W and Stewart B H Circulating and urinary catecholamines in pheochromocytoma Diagnostic and pathophysiologic implications N Engl J Med 301 68 1979
11 Ross, E J The management of cases of pheochromocytoma Clinical staff conference University College Hospital London Proc R Soc Med. 55 427 196[illegible]

mycotic aneurysm which of the possibilities that I entertained would statistically be the most likely The third consideration is a pheochromocytoma that had not been recognized While the latter is quite rare or considerably more rare than a mycotic aneurysm everything in this patient s story is compatible with that diagnosis This is because of the observations that were recorded in the last physician s note in the record of this patient and because of her spells her orthostatic symptoms and her past history of labile hyper tension

Dr Spittell s Clinical Diagnoses

1 Recent bacterial *(Streptococcus bovis)* endocarditis of the aortic valve

2 Recent aortic valve replacement

3 Perioperative cerebrovascular hemorrhage secondary to ruptured mycotic aneurysm To be ruled out are the possibilities of an unrecognized pheochromocytoma and coincidental carcinoma of the colon

Pathologic discussion

Dr Lie The autopsy was performed within 8 hours of death The immediate cause of death was indeed a cerebrovascular catastrophe The patient had a subdural hematoma over the right lateral convexity and middle fossa with compression of the right cerebral hemisphere and the rostral brainstem and uncal herniation There were also secondary hemorrhages in the midbrain and upper pontine tegmentum There were no cerebral aneurysms ruptured or unruptured

There was also hemorrhage into the anterior mediastinum (50 ml) the right pleural cavity (800 ml) and the left pleural cavity (100 ml) The heart was enlarged due to left ventricular hypertrophy weighing 680 g and there was generalized epicardial hemorrhage (Fig 3A) The aortotomy sutures were intact and the aortic valve prosthesis was securely seated With the exception of a focal 90% atherosclerotic luminal narrowing in the proximal third of the right coronary artery the extramural coronary arteries showed noncritical (< 75% luminal narrowing) atherosclerosis Scattered foci of fibrosis were present in the left ventricle Although there was no regional ischemic necrosis (myocardial infarction) foci of subendocardial myofibrillar degeneration[3] (contraction band necrosis) (Fig 3B) were widespread

Attached to the right adrenal gland was a large (8 by 6 5 by 5 cm) well circumscribed hemorrhagic tumor (Fig 4A) This tumor weighed 160 g and histologically was a pheochromocytoma (Fig 4B) A portion of the tumor was freshly frozen at the time of autopsy Subsequent chemical analyses showed that the tumor contained norepinephrine 21 8 μg/mg epinephrine 51 2 μg/mg and dopamine 0 3 μg/mg of the wet tissue

Thus we have an example of the *lethal complication of unsuspected pheochromocytoma* in a patient who had surgery for an unrelated condition namely *perioperative hypertensive crisis and hemorrhagic diathesis*

Dr Spittell Did the patient have any colonic lesion at all?

Dr Lie No nor was there any other neoplastic or endocrine lesion

Dr Olney After reviewing the patient s record in detail would you think Dr Spittell that the possibility of a pheochromocytoma was one that should have been considered by anyone caring for the patient preoperatively?

Dr Spittell We all get burned from time to time and I guess I have been burned by just about everything that burns One of the lessons I have learned is that when I have a patient who has hypertension it is always a good idea to consider the secondary forms of hypertension If I am going to send a hypertensive patient to surgery I would certainly like to have the results of urinary metanephrines

Dr Lie Pheochromocytoma is a tumor of neuroectodermal origin that arises from the chromaffin cells of the sympathoadrenal system Pheochromocytoma is not a common tumor its estimated frequency among the general population is approximately 1 per 200 000 per year In the 50 years since Dr Charles H Mayo reported the first successful surgical resection of a pheochromocytoma from this institution we now have in our autopsy files 54 patients with pheochromocytoma among the 40 078 consecutive autopsies performed in the period 1928 to 1977 This relatively high autopsy incidence of 0 13% would suggest that a significant number of these tumors may be clinically unsuspected This turned out to be precisely the case when we reviewed the records of these patients[4] The diagnosis of pheochromocytoma was not made clinically in 41 (76%) of the 54 patients Among the other 13 patients in whom the existence of a pheochromocytoma was known during life the diagnosis was

sociocultural mobility and changing life events is persuasive data from animal experiments directly and unmistakably links psychosocial disruptions to pathological changes in the cardiovascular system It is interesting that the prevalence of coronary artery disease and hypertension generally parallels the increasing complexity and ambiguity of social systems and social hierarchies whether we are speaking of animals or mankind Given the complexity of human interactions and psychology it is understandable that we should begin this discussion with the more well controlled experiments conducted in the less cognitively complex members of the animal kingdom

Work summarized by Mason[3] has shown that psychosocial stimuli can elicit either of two neuroendocrine responses One response involves arousal of the pituitary adrenal cortical system and the other that of the sympathetic adrenal medullary system Social interactions resulting in downward displacement in the social hierarchy lead to stimulation of the pituitary adrenal cortical system with mental depression decreased gonadotropin levels enhanced vagal activity, gluconeogenesis and pepsin production In contrast the sympathetic adrenal medullary system is called into play as agonistic or competitive behavior is invoked in an attempt to maintain status and prevent threatened loss of esteem and/or related objects of attachment

A variety of behavioral paradigms have been examined with regard to their influence upon the cardiovascular system in a variety of species Such animal experiments have included classical conditioning avoidance conditioning avoidance yoke procedure pre avoidance experience and psychosocial stress

Classical conditioning In Pavlovian or classical conditioning experiments a relatively neutral stimulus called a conditioned stimulus is immediately followed by another stimulus called the unconditioned stimulus After repeated pairing of conditioned stimulus followed by unconditioned stimulus the originally neutral stimulus comes to elicit a pronounced physiologic response Classically the conditioned stimulus has been a light or tone and the eliciting or unconditioned stimulus has been an aversive stimulus such as electrical shock. Yet it has been observed that when monkeys are given relatively long periods of habituation to restraining chairs with gradual shaping of responses and training sequences that minimize the ambiguity of stimulus cues the baseline he[...] rate during conditioning sessions can genera[...] kept near or even below the intrinsic rate[...] contrast when experimentally naive monkeys[...] given short periods of habituation with l[...] numbers of trials or training sequences that[...] not minimize ambiguity the pretrial base[...] heart rate is significantly in excess of the [...] value[4] In classical conditioning therefore, no[...] ty appears to be an important element. [...] noshvili and others[5] presented three rhesus m[...] keys with a number of stressful behavioral s[...] tions over a period of two years. The [...] prominent behavioral procedure was one in wh[...] a light signal followed by a shock was super[...] posed upon a bar press response for food. Du[...] the first four months on the training schedule, [...] investigators observed that blood pressure [...] creased from baseline levels but subsequen[...] sustained increase in blood pressure beg[...] develop When the animals developed ne[...] behavior the normal diurnal pattern in w[...] blood pressure heart rate and breathing [...] were greater during the day than at night be[...] altered and the authors observed that the ap[...] were out of phase

Avoidance conditioning In the avoidance [...] ditioning experiment the animal is traine[...] avoid stimulation by making a desig[...] response During signalled avoidance the [...] nism is warned that it must make a desig[...] response to avoid being shocked. In unsig[...] avoidance the animal is required to press a l[...] at a prescribed interval to avoid recur[...] shock A variety of animals engaged in avoid[...] conditioning reveal an increase in arterial [...] sure associated with an increase in heart rate[...] cardiac output and variable changes in perip[...] resistance Several investigators [...] have [...] onstrated changes in cardiac electrophysio[...] properties during avoidance conditioning [...] alterations have been implicated in diverse [...] diac arrhythmias including ventricular fib[...] tion Ernst and associates[11] using avoidance [...] ditioning trained dogs to diminish coronary [...] flow which uncoupled from other cardiovas[...] variables as training proceeded, demonstr[...] that coronary circulation can be independ[...] controlled by a stressful behavioral contin[...]

Avoidance yoke procedure In the avoid[...] yoke procedure the avoidance animal is tr[...] to manipulate a lever to avoid shock. Whe[...]

Fundamentals of clinical cardiology

Psychosocial and behavioral influences in the pathogenesis of acquired cardiovascular disease

James C Buell MD *
Robert S Eliot M D F A C C **
Omaha Nebr

Curiously the concept that man s circumstances and emotions importantly influenced his circulation were long ago accepted by observant students of mankind Indeed few folklore notions have enjoyed as widespread and persistent popularity as those that ascribe sudden death to emotional shock Throughout history anecdotes appear about people dying suddenly in the throes of fear rage grief humilation or joy Yet with the ebb and flow of medical progress in the last century scientific measurement and laboratory observation assumed increasing importance in the evolution of medicine and such anecdotes held little sway in the scientific community Now history repeats itself and age old observations are being reexamined as a sizable body of evidence accumulates implicating psychosocial conflict emotions and behavioral patterns in the pathogenesis of coronary heart disease sudden death cardiac arrhythmias and systemic hypertension This interest has been heightened in investigations of coronary heart disease by the observation that the traditional risk factors fail to account for half of the cases of clinical coronary heart disease encountered on a worldwide basis

It is difficult to separate the role of behavior and environment from the accepted risk factors

From th Omaha Veterans Administrati n Medical Ce ter and th Division of Cardio ascular Medicine University of Nebraska Medical Cente Omaha Nebr

Received for publication Mar 5 1980

Reprint requests James C B ell, M D Chief Cardiol gy Omaha V.A. Med al Center 4101 Woolworth Omaha, N br 68105

*Chief of Cardiol gy Omaha V A. Med cal Center and Assistant Professo of Medicine, Cardiovascular Center Uni ersity f N braska Medical Center Omaha.

**Professor of Medicin and Direct C rd o ascul C nter Uni e sity of N braska Med c l Cent r Omaha

000?-8 03/60/110?23 + 18$01.80/0 © 1980 The C V Mosby Co

Each risk factor is a composite of genetic environmental and behavioral components which can all be provoked enhanced or sustained by influences which are beyond simple metabolic or pathophysiologic explanations Thus in view of our incomplete knowledge of the pathogenesis of coronary heart disease and the likelihood that additional key factors are operating it is not surprising that preventive measures confined to a few factors have met with limited success to date The recent acceptance of Rosenman and Fried man s Type A behavior pattern as a statistically validated major risk factor is but one example of medical interest in psychosocial and behavioral influences In point of fact the results from most of the reported epidemiologic studies that generally incriminate the high fat intake of upper middle class Western man as the major cause of elevated serum cholesterol could just as well have been utilized to support the concept that rapid industrialization and the resultant socioeconomic stress were the responsible factors In addition to dietary intake and tobacco usage the lifestyle and society of Western industrialized man is distinctly different from that of populations manifesting a lower incidence of coronary heart disease While a complete understanding of how such influences participate in and are interrelated with other factors in the pathogenesis of cardiovascular disease remains the work of future investigation this work appears warranted on the basis of what is known and suspected

Psychosocial and behavioral influences in cardiovascular disease in animals

Whereas epidemiologic evidence linking coronary and hypertensive heart disease with prolonged emotional stress behavioral patterns

second is the brain stem hypothalamic system which is concerned with sex hunger, thirst and sleep drives It is at the level of cognitive integration however, where species differences become most apparent and this process involves the frontal association cortex and the parietal and temporal cross modal association areas termed the sociocultural brain Only in man do these structures attain such overwhelming proportions when compared to the rest of the brain

Nevertheless the strongest evidence for a potential or substantiated influence of psychosocial and behavioral factors in the pathogenesis of cardiovascular disease in man rests with manipulations of the social hierarchy and interactions of designated animal species Henry and Ely have demonstrated that fixed hypertension and myocardial hypertrophy progressive arteriosclerosis myocardial fibrosis and renal failure can be induced in socially deprived mice by subjecting them to social interaction Moreover Henry and Ely have shown that at least some of these changes were apparently mediated by an increase in the adrenal enzymes tyrosine hydroxylase and phenylethanolamine N methyltransferase The increases observed appeared to reflect a situation in which brief sympathetic discharges elicited by discontinuous emotional stimuli were transformed into sustained sympathetic arousal An important observation in addition to the impact of social manipulation is the fact that different genetic strains of mice have different levels of blood pressure and different potentials for synthesizing adrenal catecholamines They also have different temperaments responding differently in degree to the same social paradigm Thus the physiologic consequences of psychosocial provocation are largely engrafted upon a foundation of cultural and genetic predisposition

Von Holst in experiments with tree shrews introduced a subordinate animal to another male who was an experienced fighter After the subjugated animals were separated from the experienced fighters by a wire mesh but were allowed to continue to observe each other the subordinates would fall into comas within 2 to 16 days despite adequate food and drink and would die in uremia due to renal insufficiency Until the time of death the uremic subordinates manifested continuous piloerection as a manifestation of sustained sympathetic arousal Lapin and Cherkovich performed similar experiments in which they altered the social situation of dominant Hamadryas male baboons The male of this particular species adopts its females when they are still immature and develops an intense attachment for them When the dominant male was separated from his mate and another male was put into the female's cage in full view of the former consort, the displaced maled showed intense agitation After several months hypertension and other evidence of chronic cardiovascular disease developed in the original consort While some of the studies were aimed at developing experimental neuroses rather than deliberate cardiovascular disease the authors encountered a significant number of cases of hypertension coronary insufficiency and acute myocardial infarction

Ratcliffe[21] in studies at the Philadelphia Zoo observed that deaths in animals and birds from arteriosclerotic coronary heart disease increased from an incidence of less than 1% in 1949 to more than 10% in 1968 Diet and mean age at death were no different but he did note that in 1949 the zoo began an attempt to assemble family groups This contrived social grouping resulted in conflicts breeding failures and abnormal behavior within the family groups" He eventually concluded that the increase in coronary heart disease resulted from behavioral responses in these social situations He then did an experimental follow up studying the psychological responses of swine to separations occurring after the primary social bonds of grouped animals had been formed At the end of a year the separated animals showed a significantly greater incidence, extent and severity of coronary atherosclerosis Whereas grouped and paired swine responded to human visitors with friendly grunts and squeals for a handout those swine that had been separated especially the normally friendly females failed to respond to visitors and even refused offers of added corn

Weber and Vander Walt produced cardiomyopathy in New Zealand white rabbits by alternately housing them singly and then crowding them again In the course of ten months 30 of the animals had expired with ten dying during the first week ten more during the first month and the rest at intervals during the succeeding months In those dying within a few days, severe myocardial necrosis was observed in the subendocardium and myocardium Those that survived longer developed foci of myocardial fibrosis and

the animal fails to meet the scheduled requirement both the animal and its yoked partner receive shocks Thus both animals always receive the same number and temporal pattern of shocks but only the avoidance animal has control over whether shock will occur In such experiments Corley and colleagues[12] observed that five of six "yoked" monkeys developed physical deterioration and severe bradycardia with ventricular arrest but no significant myocardial necrosis In contrast, the avoidance monkeys developed electrocardiographic abnormalities and myocardial degenerative lesions Such unsignalled avoidance can activate the sympathetic autonomic nervous system yielding a direct action of norepinephrine upon beta receptors in the myocardium which results in myocardial necrosis Richter[3] demonstrated the adverse consequences of yoked helplessness when he demonstrated that rats developed fatal vagally mediated bradycardia after being subjected to severe unavoidable water stress Interestingly Schneider observed that among patients who had a past myocardial infarction those with the greatest tendency to bradycardia in response to startle also had the poorest prognosis In Corley and associates experiments[2] the key difference leading to divergent pathologies was that the animals in the avoid condition had control over whether they received shock but the yoked animals did not Also the occurrence of shock was somewhat predictable in the avoid but unpredictable in the yoked condition.

Preavoidance experience Animals subjected to repeated sessions of avoidance conditioning eventually had changes in their baseline cardiovascular physiology during the period immediately preceding the session Such prior experience can influence the organism s behavioral physiological and biochemical responses Anderson and Tosheff[5] studied the cardiovascular responses of dogs during daily sessions consisting of a one hour anticipation period followed by an hour of unsignalled shock avoidance When the animals were placed in a harness for the hour immediately preceding the daily sessions of unsignalled avoidance the animals manifested a progressive decrease in heart rate and cardiac output accompanied by a progressive increase in total peripheral resistance Studies by Adams and co workers using cat fight confrontations with glass partitioned separation demonstrated that shortly before the episodes of fighting began both heart rate and cardiac output decreased while total peripheral resistance increased These studies suggest that during an orienting reflex total peripheral resistance increases The orienting reflex response is hemodynamically similar to the diving reflex and has been elicited by electrical stimulation of the brain stem in rats[1] This reflex pattern has been suggested as one mechanism for sudden death as manifested in the experiments of Corley and associates[2] using monkeys and Richter[3] using rats Such studies have resulted in the concept of learned helplessness According to the learned helplessness hypothesis animals exposed to a stressor they cannot control may learn that their behavior cannot control the environment The biochemical explanation for this behavior appears to involve depletion of brain norepinephrine Glazer and co workers[17] found that depletion of monoamines by a single injection of tetrabenazine produced a depressed response to escape in rats when the avoidance escape response involved a relatively high degree of motor activity but not when a minimum of motor activity was required These investigators also observed that by decreasing the stress induced depletion of monoamines by the use of an MAO inhibitor they could protect the animals from the effects of inescapable shock Thus the MAO inhibitor reduced the learned helplessness produced by unavoidable shocks. Studies of cardiac somatic coupling by Obrist and colleagues[8] have indicated that vagally mediated reflexive bradycardia occurs in sympathetically aroused animals when these animals inhibit their somatic activity The vagally mediated cardiac component of the baroreceptor reflex is sufficiently strong to override the concomitant sympathetic activation of the heart[19]

Psychosocial stress The constellation of influences in cardiovascular disease most clearly approximating those seen in man occur during experiments involving manipulation of the social hierarchy of animal colonies So far we have discussed a variety of experimental methods resulting in diverse neuroendocrine responses which may be elicited singularly sequentially or in concert These responses are mediated on the effective integrative level through two major pathways The first is the limbic striatal system which is involved in the social emotional and selfpreservation behavior of animal species The

costeroid levels which were originally high showed progressive decline while epinephrine and norepinephrine levels showed progressive upward trends This suggests that the rat altered its response to the experience Early immobilization might be regarded as a threat against which the animal was helpless had no coping defenses and a perception of loss of control However with repetition although the event was equally noxious it was perceived as having a predictable outcome Thus there are three major indications from experimental data

1 Animal studies demonstrate that as a result of emotional arousal purely cognitive processes can lead to neuroendocrine changes of the adrenal medullary and/or adrenocortical systems and that dependent upon the environmental situation and coping mechanisms available such responses may be elicited singularly sequentially, or in concert

2 Different psychosocial and physiological changes develop according to the emotion predominantly concerned Anger challenge and fear are associated with the fight or flight response and sympathetic adrenal medullary activation with the familiar chain of physiological changes

3 Depression is found in situations fraught with loss of control such as feelings of helplessness and subordination In contrast it involves activation of the pituitary adrenocortical system and depression of gonadotropins

The clinical relevance of these observations is supported by Bourne s studies[29] of men during combat in Vietnam and by Katz and colleagues studies[30] of women awaiting biopsy reports of a lump in the breast Both studies showed that feelings of social acceptance and high personal worth which commonly accompany effective psychiatric defenses are associated with decreased activity of the pituitary adrenocortical system Carroll s[31] work complemented these studies and demonstrated that primary depression accompanied by lack of self worth was associated with the reverse response of increased activation of the adrenal cortex

In addition there is an increasing amount of experimental evidence linking the central nervous system to lipid metabolism and atherosclerosis Chronic stimulation of the ventral medial nucleus of the hypothalamus of cholesterol fed rabbits significantly elevated plasma cholesterol levels[3] and exposure to a continuous auditory stimulus of white noise induced enhanced alimentary hyperlipemia in rats and rabbits[34] An invol ment of adrenal gland activity in the lipem response to auditory stimuli has been noted the finding that such stimuli induce a mark increase in adrenocortical steroid secretion, a this activity may persist for some weeks af exposure to auditory stimuli On the other ha removal of the adrenal glands and the hypophy did not abolish the milieu induced postprand hyperlipemia of fat fed rats[3] However an el trolytic lesion placed in the anterior hypotha mus does prevent the milieu induced postpr dial hyperlipemia otherwise observed in th animals Hypercholesterolemia can be induced rats by bilateral injury of the ventral med nuclei of the fornices and the medial portion the lateral hypothalamic nuclei, but cannot ascribed to any change in function of the thyr adrenals testes or pituitary that might have b induced by the hypothalamic lesion nor can it ascribed to any induced derangement of p creatic discharge of insulin[35]

Studies of spontaneous vascular lesions in a mals yield important information which is use in assessing the role of various risk factors in process of atherosclerosis Such animal stu provide baseline data for comparison with exp mentally induced arterial lesions in that spe and also provide a panorama of the types lesions which may occur in the *animal* kingd They yield insight into the pathogenesis of art al disease in particular species provide infor tion regarding the types of *lesions* occur throughout the animal kingdom and permit mulation of hypotheses concerning arterial ease in general

Stout and Bohorquez[36] have reported that t cal atherosclerotic plaques are *common* in b being found in 24% of the aortas The prevale of aortic atherosclerosis in birds could not correlated with the type of *diet* consumed captivity or in nature Fatty streaks and fibr plaques are quite common in many specie mammals and birds In seals and sea lions ao fibrous plaques are plentiful and similar in m phology and distribution to *those* occurring humans[36] However the fibrous plaque in s contains no stainable lipid indicating that s mechanism other than *lipid* insudation responsible for the proliferation of intu smooth muscle cells The demonstration o striking correlation between the developmen the lesions and the *locale* of hemodynamic fo

compensatory myocardial hypertrophy in the fibers adjacent to the fibrotic areas

The previous discussion provides ample evidence that environmental novelty and/or adversity particularly when sustained is capable of eliciting physiologic responses which when unabated may lead to pathologic consequences In addition psychosocial interactions are powerful and important influences in eliciting such responses Henry and Ely[9] have pointed out however that social stimuli do not act directly on the individual Rather perception of the social environment as mediated by personality role and status variables arouses emotions which induce physiologic responses An important aspect of such discussions is that in addition to the impact of social manipulation different genetic strains have different levels of blood pressure and different potentials for synthesizing adrenal catecholamines They also have different temperaments responding differently in degree to the same social paradigm Thus the physiologic consequences of psychosocial provocation are largely engrafted upon a foundation of cultural and genetic predisposition and are effected principally through cognitive mechanisms

It is known that stress such as cold heat fasting or exercise fails to elicit typical neuroendocrine responses of either the sympathetic adrenal medullary or pituitary adrenocortical systems if emotional arousal is avoided[26] This has been illustrated in early studies of the effects of three day fasting on two of eight monkeys housed in the same room The deprived monkeys often vocalized in apparent protest when the caretaker handed food pellets to the others The elevation of 17 hydroxycorticosteroids on the first day of the fast suggested that psychological as well as nutritional factors might be at work since the fasting monkeys were exposed to all the sights sounds and stimuli associated with routine feedings and the presence of the nonfasting monkeys If novelty and uncertainty were carefully minimized by allowing the monkeys time to adapt to experimental conditions outside stimuli eliminated by soundproofing and discomfort minimized by giving the monkeys non nourishing fruit flavored pellets no change in steroid levels occurred during fasting periods These sorts of studies strongly suggest that rather than social stimuli acting directly on an individual personal assessment of the social environment uniquely refracted through one s self image and value perceptions arouses emotions which produce physiologic responses

Within the society whether animal or man a hierarchy exists and approved behavior must be exercised It is not only man who responds to a life situation by how it affects him personally a monkey whose parents are dominant members of a troop is likely to attempt a dominant role Socially deprived and formerly isolated animals that give vent to their irritation at the expense of an infant or a more dominant group member receive short shrift from the infant s parents or an offended social superior A well adapted subordinate of any species knows he must wait his turn patiently and show respect for those higher in social rank If a psychosocial stimulus is inhibited at higher levels by interaction with coping patterns it will be perceived as irrevelant within the frame of reference If perceived as relevant however arousal is triggered and limbic system components respond initiating further trains of responses

Studying dominant and subordinate males in mouse colonies Ely and Henry verified that change of status is associated with altered neuroendocrine patterns. They demonstrated that the enzyme tyrosine hydroxylase which is under sympathetic control and the rate limiting enzyme in the synthesis of norepinephrine rose more markedly in dominant mice than in subordinates as struggle for status in the newly formed social hierarchy progressed Phenylethanolamine N methyltransferase which converts norepinephrine to epinephrine not only increased in dominant animals but continued to rise while falling in subordinates as they adapted to a loss of status Once the mice adapted to each other in the colonies these changes were no longer seen during later stages of interaction as the social hierarchy stablized On the other hand during the unstable phase of the social hierarchy subordinates demonstrated marked increases in plasma cortisol levels which returned to normal levels when the social hierarchy became stable and established Whereas challenge and anxiety elicit sympathetic and adrenal medullary responses loss of control and depression are associated predominatly with corticosteroid responses Studies indicate that a gradual shift occurs in the nature of a rat s response to immobilization when taped to a laboratory bench With repeated experience corti

per capita consumption of alcohol Some of the recognized factors contributing to the psycholog ical distress in this society were (1) the perceived national urgency of putting a man on the moon by the end of 1969 (2) the great national and international visibility of the Center in which a dramatic failure would have adverse occupational consequences (3) the problems of interpreting and coordinating the work of approximately 300 different major industrial contractors particular ly for administrators and managerial personnel engaged in interorganization liaison (4) the pro gressive decline in budget and employment and (5) the resultant threat of loss of employment identity and income from lack of demand for overspecialized and highly trained skills inappro priate to the common marketplace In short the project demanded an ever increasing if not fren zied pace of production with the ultimate reward of nearly inevitable dismissal financial loss and loss of professional identity

There were findings of an unusually high per cent of abnormal resting electrocardiograms [30] In addition there was a remarkable incidence of psychoneuroticism anxiety and depression with in the population [31] Postmortem myocardial his tologic features of victims of sudden death dem onstrated the existence of hyperfunctional anomalous contraction bands This same histo logic picture of hyperfunctional necrosis can be quickly induced in the hearts of animals by the administration of boluses of catecholamines [32] The abilities of catecholamines to facilitate rhythm disturbances increase myocardial oxygen demand augment vascular reactivity and mobil ize free fatty acids are well established facts The results of animal experimentation have demon strated the protective effect of pretreatment with beta blockade and recent studies suggest that beta blocker therapy has a beneficial impact upon the incidence of coronary death in some coun tries Many years ago Raab maintained that corticosteroid administration potentiated and augmented the myocardial degenerative in fluences of catecholamine administration in ani mals Animal experimentation strongly suggests that the combination of heightened sympathetic arousal followed by a complete sense of hopeless ness and helplessness is a particularly lethal combination for the development of sudden death [35] In a national sense the KSC workers were struggling winners who finally did achieve in putting a man on the moon In a personal and professional sense the inevitable dismissal and loss of professional and financial security resulted whether they succeeded or failed at their mission This placed many of them in a situation of being ultimate losers in a joyless struggle For most highly specialized aerospace personnel the Kennedy Space Center experience was an overall Pyrrhic victory on a personal level. The combined factors of arousal struggle loss and helplessness are clearly evident in retrospect in this study and are hauntingly reminiscent of a multitude of experiments employing yoked and restrained animals

A large number of experimental animal studies have strongly implicated psychological stress in the precipitation of arrhythmias and sudden death Several reports have recently appeared in the literature documenting the effects of psychological stress in lowering the threshhold for ventricular fibrillation and sudden death both in animals and in man [3, 34, 37] The combination of arousal with enforced helplessness and extreme conflicting stimulation has been demonstrated by Gelhorn [3] to result in breakdown of the reciprocity between the fight or flight reaction and the playing dead reaction Under overwhelming stress both systems become active simultaneously or in rapid alternation with each other This constitutes the neurophysiologic basis for the behavioral disorganization typically exhibited by animals under extreme stress the dog that struggles crouches trembles moves about aimlessly barks whines salivates urinates, defecates pants piloerects and sometimes momentarily dozes All these activities indicate simultaneous or rapidly alternating sympathetic parasympathetic activation

Although it is difficult to conduct controlled human studies comparable to those readily obtained in animals electrocardiographic monitoring during a variety of psychologically stressful tasks in humans has documented significant and potentially fatal rhythm disturbances in direct association with episodes of emotional stress [9] Thus it appears that continuous ECG monitoring can provide previously unavailable physiologic data on the process of dying Advancing technology is beginning to illuminate pathophysiologic processes which may offer guidance to the factors which can lead to lethal consequences and techniques suitable for their control. Of

uggests that mechanical stress may be an impor ant operative factor Stout and colleagues[37] have lso demonstrated that chronic low intensity lectric shock is associated with an increased roliferation of aortic fibrous plaques in minia ure pigs While many investigators feel that entral plaque necrosis in human atherosclerosis s due to accumulation of lipids within the cells of he plaque atherosclerotic plaques of giant nteaters and aardvarks manifest central plaque ecrosis before lipid accumulation[38] Moreover requent areas of focal plaque necrosis apparently nvolving smooth muscles were found within brous plaques in a number of species These reas of focal necrosis were also present within brous plaques of experimental pigs receiving hronic electric shock

It is apparent from the foregoing discussion hat atherosclerosis presents manifold counte iances but is relatively commonplace in the animal kingdom However captive birds seem to show a higher incidence of atherosclerosis per iaps because of their higher blood pressures and erum cholesterol levels

Regarding the influence of serum lipids in the therosclerotic process it has been shown that here is a bidirectional transfer of cholesterol in normal aorta with equal movement of lipid in and out of the endothelium However when the inti na becomes abnormal lipid movement into the rterial wall predominates Superimposed upon he ubiquitous atherosclerotic lesion are species pecific factors It seems that attributes of a pecies are a preponderant factor in the develop nent of atherosclerosis It is certain that being a ird is more important than the type of diet onsumed since graminivorous birds have far more atherosclerosis than do graminivorous ani nals and so on A unique peculiarity of human therosclerosis is the sequela of thrombus forma ion and this implies that platelet aggregation lays a significant role in the ischemic sequelae It s against this background of animal and experi nental information that the role of psychosocial actors stress and behavior in the pathogenesis of ontemporary clinical cardiovascular disease will e viewed and discussed

linical cardiovascular disease

We may look at cardiovascular disease in terms f distinct entities such as hypertension coronary eart disease and sudden death but we must ecognize that they seldom stand in isolation and that overlapping relationships exist The clinical observations linking psychosocial environmental and behavioral factors with atherosclerotic and hypertensive cardiovascular disease arrhythmo- genesis and sudden death are too extensive to permit a comprehensive discussion within the scope of this review and the reader is referred to a number of reviews in the literature[3] [4] We will briefly highlight some observations regarding psy chosocial and behavioral factors as they relate to sudden death coronary heart disease and hyper tension These will then be synthesized into a composite of hypothetical mechanisms that may interrelate the accepted risk factors

Sudden death

Few folklore notions have enjoyed as wide spread and persistent popularity as those that ascribe sudden death to emotional shock Far back in recorded history people are described as dying during emotional upheaval Almost 2 000 years ago Celsus[5] described that emotional states could influence the heart William Har vey[5] reaffirmed the observation in 1628 by stat ing that fear and every affection of the mind that is attended by either pain or pleasure hope or fear is the cause of an agitation whose influence extends to the heart In more recent times such influences have been causally implied by Hunt er s prediction of the circumstances of his death and by Cannon s observations on voodoo death Even Osler[4] commented on the behavioral aspects of sudden coronary death in his straight forward and simple description of the coronary prone individual as a keen and ambitious man the indicator of whose engines is set at full speed ahead However with the advent of scientific medicine in the late nineteenth century such observations fell into disrepute as scientific and traditional medical approaches dictated that the cause of death should be established at the necropsy table and in the laboratory

As an epidemiologic phenomenon the inci dence of sudden death at the Kennedy Space Center during the mid 1960 s strongly suggested the influence of psychosocial and behavioral fac tors Although traditional risk factors were not remarkable the sudden death rate among men at the Kennedy Space Center (KSC) was nearly 50% higher than that of age and sex matched control groups (Warheit and Eliot unpublished manu script) The divorce rate was three out of four marriages and this microcosm led the nation in

members of the cohort. The diets of all the chimpanzees contained 10% of total calories as fat. Both animals manifesting predominant coronary and cerebral atherosclerosis had adjusted poorly to captivity, showing neurotic traits such as stereotyped posturing, hoarding of food and other objects, and poor socialization with peer animals in the colony.

While dietary fat intake appears to be statistically important, the documented observations that dietary cholesterol is limited in absorption and that most cholesterol is manufactured in the liver suggests that other factors might be importantly involved. It is curious that Friedman and colleagues studies[43] of accountants demonstrated that their highest serum cholesterol levels consistently occurred during periods of severe occupational and emotional stress. Conversely, minimal values occurred during periods of minimal stress despite unchanged levels of dietary fat intake. While fat feeding rabbits to produce atherosclerosis has been carried out as a reliable animal model for the last 60 years, Nerem[44] reports that if the animals are fondled or given daily doses of diazepam, the extent of atherosclerosis is significantly reduced despite comparable levels of attained hypercholesterolemia. Thus, the association between dietary intake of fat and atherosclerosis is an incomplete association. One should recognize that the dietary hypothesis arose primarily from studies involving prosperous industrialized competitive societies and restrained, fat fed, socially isolated animal models.

A third risk factor is cigarette smoking, and there is little question that carbon monoxide inhalation and nicotine exposure have definite physiologic consequences. Nicotine is a stimulator of both sympathetic and parasympathetic ganglia and increases the arterial epinephrine concentrations in man. Nicotine also induces ADH secretion, liberates catecholamines from the heart, increases heart rate and cardiac output, lowers the threshold for ventricular fibrillation and causes peripheral vessel constriction. Nicotine increases free fatty acids in serum through its catecholamine release and usually promotes the development of atherosclerotic lesions in fat fed animals.[45] Necrosis and calcification of the medial layers of aorta were often seen in these animals and this might be explained by an effect of catecholamines since their administration to animals has a similar effect. The effect, if any, of smoking on blood coagulation and the function of platelets is probably related to an action of nicotine since carbon monoxide exposure does seem to have any effect. Carbon monoxide does induce arterial hypoxia which accelerates atherosclerosis in cholesterol fed rabbits.[46] There is no qualitative difference between lesions in animals exposed to carbon monoxide and animals exposed to hypoxia.

However, in addition to powerful physiologic effects, it is obvious that smoking constitutes a cultural and behavioral phenomenon as well. In Keys' seven country study,[47] the findings were that nonsmokers consistently differed from smokers in being relatively heavier and fatter and tended to have higher blood pressures, except in Japan where there was no consistent difference. Light smokers tended to have lower serum cholesterol values than their fellows in the same sample, but otherwise serum cholesterol showed little or no relationship to smoking habits in most areas. Exceptions were in Slovonia, Montenegro, Crete, and Corfu where nonsmokers tended to have higher cholesterol values and in Velika Krsna, Yugoslavia, where the opposite tendency prevailed. In general, the higher blood pressures in the nonsmokers could not be explained by the excess of obese men in this group. Indeed, the high prevalence of smoking in Corfu and Japan correlated negatively with electrocardiographic findings of coronary heart disease, a statistical anomaly at variance with studies of United States populations.

There are obvious health reasons for discouraging the smoking habit, yet it appears obvious that genetic and sociocultural behaviors might participate in modifying results in the etiologic relationship between cigarette smoking and atherosclerotic coronary heart disease. In addition to its identity as a risk factor, cigarette smoking is a sociocultural behavior which in some societies and cultures is negatively or insignificantly correlated with atherosclerosis. These comments are not intended to minimize the health consequences of the smoking habit but merely to point out that despite the powerful physiologic effects of tobacco smoke, there is not an immutable relationship with coronary heart disease in all populations, cultures and societies. In studying this risk factor's relationship to coronary atherosclerosis, the sociocultural and motivational aspects of the habit should be examined in addition to its prevalence.

An additional link to be considered in the

perhaps equal importance is the fact that animal studies have taught us that the same experimental environments may produce different results in different species dependent upon genetic experiential and cognitive functions. Different results may also be obtained by altering time frames or options within animals of the same species. Such findings indicate that the impact and countenance of a psychosocial stimulus in the human as in various animal species, is related to individual cognitive functions circumstantial novelty and psychological defenses. The likelihood of an event eliciting an adverse physiologic response depends also upon a complex amalgam of factors including genetic predisposition early social experience and a lifelong process of conditioning and cultural factors.

Therefore, we believe that ambulatory monitoring as a measure of physiologic response should be correlated with aspects of cognitive behavior. The influence of psychosocial and behavioral factors is becoming increasingly well substantiated in the clinical areas of arrhythmogenesis and sudden death. A variety of physiologic mechanisms contributing to these clinical phenomena are being discovered and examined. The aspects of cognitive integration eliciting such responses remain an important frontier for further investigation.

Atherosclerotic coronary heart disease

While the link between observed environmental provocation and physiologic response is relatively immediate and direct in studies of sudden death the role of psychosocial and behavioral factors in coronary heart disease is far more complex and elusive yet these appear to be culpable. Considering the slow evolution of clinical coronary heart disease and our incomplete knowledge of the pathophysiology of atherosclerosis and the mechanisms of its sequelae one can hardly expect more proof than guilt by association. Because we really do not fully understand the mechanism whereby any heretofore commonly accepted coronary risk factor effects arterial damage we still have to determine the intrinsic biophysical metabolic and neurochemical processes which over prolonged periods of time eventuate in the onset of clinical coronary heart disease. When such fundamental mechanisms are understood it should not be too difficult to track down the precise cardiopathic pathways which might be fostered by psychosocial and behavioral factors.

At the present state of our understanding it appears that the atherosclerotic process involves injury and proliferation of intimal smooth cells with subsequent alteration in permeability and/or metabolism and tends to occur at bifurcating or originating sites of vessel branches. With the progressive insudation of lipid material hemodynamic impairment to flow eventually results. The site of lesion formation suggests that hydrodynamic stress and shear forces participate in the process. This also suggests that the higher and more frequent the kinetic energy trauma to the circulation at these points of turbulence the more rapid the evolution of the lesion. While these findings are consistent with hypertension as a risk factor it is obvious that additional factors are operative. Those individuals possessing the $C3^F$ gene in essential hypertension have a coronary risk rate nearly seven times higher than those who are $C3^F$ negative. Furthermore epidemiologic studies in Japan suggest that in some populations the incidence of hypertension may be remarkably high without a concomitant increase in atherosclerotic findings. Thus the association is incomplete but it is generally accepted that elevated blood pressure and increased shearing forces constitute an aggravating cause in the development of atherosclerosis. The behavioral aspects of hypertension will be discussed later.

A second factor having obvious face validity is that enhanced lipid availability is an integral part of the atherosclerotic process. Here also psychosocial and behavioral factors appear to be involved. Dietary fat intake has long been incriminated as the major factor in this process notably through some epidemiologic studies and by fat feeding various animal species. Nevertheless several observations suggest that dietary fat intake is not exclusively related to the process. Andrus and associates published one attempt to induce atherosclerosis in chimpanzees through high fat high cholesterol feeding. In that study it was interesting that although there were more aortic fatty streaks in the experimental animals than in controls this difference was less pronounced in the epicardial coronary arteries and there was no difference in the cerebral arteries. Stout and Bohorquez[7] found epicardial and cerebral atherosclerosis in two of their chimpanzees which was significantly advanced over that found in other

2 Serum lipids whether available through dietary substrate or mobilized by central nervous system factors enhance and foster smooth muscle cell proliferation and become incorporated within the proliferative and necrotic lesion

3 The smoking habit through its nicotine effects on catecholamine excretion and consequent physiologic effects in collaboration with the effects of carbon monoxide upon vascular permeability tends to promote mechanisms contributing to atherogenesis

4 Platelet mobilization and aggregation directed toward areas of endothelial trauma release a platelet derived growth factor and the vasospastic agent thromboxane A_2 contributing to smooth cell proliferation in combination with vasoactive constriction

Many of the incriminated mechanisms appear to work through or are activated by catecholamines in concert with hyperlipemia Catecholamines are probably the most important factors promoting lipid mobilization They are effective in mobilizing lipid from adipose tissue both by their liberation from non adrenergic nerve terminals in adipose tissue and by their secretion from the adrenal medulla into the blood The free fatty acids not stored or utilized in the production of energy are eventually taken up by the adipose tissues or by the liver Free fatty acids taken up by the liver are formed into triglycerides and are secreted as components of very low density lipoproteins The rate at which the liver secretes very low density lipoproteins is determined partly by the rate it synthesizes free fatty acids from carbohydrates and partly by the rate it receives free fatty acids in the blood In the fasting state the secretion of very low density lipoproteins by the liver is determined principally by the levels of free fatty acids in the blood These levels in turn are determined principally by the effects of catecholamines on adipose tissue and by the rates of energy production Catecholamines promote platelet adhesiveness and aggregation promote arrhythmias and lower the threshold to arrhythmia generation and increase secretion of glucagon thyroxin calcitonin parathormone renin erythropoietin and gastrin while diminishing insulin secretion Glucocorticoids convert protein into carbohydrate and fat have a minor antagonistic effect on insulin promote the development of diabetes foster hyperlipidemia and hypercholesterolemia enhance water diuresis diminish circulating lymphocytes reduce leukocytosis and polycythemia increase platelet counts with an enhancement of clotting tendencies lower the electrical excitation threshold of the brain increase gastric acidity and pepsin production block growth hormone secretion decrease calcium absorption enhance angiotensinogen production sensitize arterioles to the pressor effect of catecholamines and decrease the inflammatory response Accelerated atherosclerosis is one of the main causes of death in Cushing's syndrome whereas the sequelae of pheochromocytoma include hypertensive crises myocardial infarction with or without coronary disease arrhythmias and catecholamine myocarditis Both of these endocrine excesses have been demonstrated to occur in reactions to various psychosocial circumstances mediated by cognitive perceptions

Type A behavior

The term Type A behavior was coined by Friedman and Rosenman almost two decades ago, but the association between a typical behavioral pattern and victims of coronary heart disease had been previously recognized by others including Osler's succinct description at the turn of the century A recent conference sponsored by the National Heart Lung and Blood Institute appraised the role of behavior as a predictor of potential coronary heart disease The review panel convened by this Institute accepted the available body of scientific evidence as demonstrating that Type A behavior as defined by the structured interview used in the Western Collaborative Group Study, the Jenkins Activity Survey and the Framingham Type A behavioral scale was associated with an increased risk of clinically apparent coronary heart disease in middle aged U S citizens The risk was found to be beyond that imposed by age elevated systolic blood pressure serum cholesterol, or cigarette smoking and appeared to be of at least the same order of magnitude as the relative risks associated with the latter three of these factors

Type A behavior was described as an aroused state superimposed on a complex underlying substrate of interrelated factors Metaphorically it can be viewed as an iceberg with a small portion apparent above the surface Unfortunately situational or environmental determinants, individual perceptive or cognitive differences and other psy

atherosclerotic chain of events is the role of platelets and thrombosis This phenomenon appears to be distinctive for atherogenic sequelae in man as compared to the rest of the animal kingdom If smooth muscle cell proliferation lipid accumulation and thrombosis are parts of the atherosclerotic mosaic clotting and platelet function must be suspected as potentially culpable agents in the process It has been suggested that repeated or chronic endothelial cell loss may be the principal event leading to atherosclerosis[66] Furthermore the intimal lesions that occur in homocysteine induced or mechanically induced arteriosclerosis can be prevented by pharmacologic agents that interrupt platelet consumption or by inducing a thrombocytopenia with an anti serum of platelets[67] The endothelium normally regulates the entrance of low density lipoproteins (LDL) the principal cholesterol carrying lipoprotein of the plasma into the artery wall Low density lipoproteins also support smooth muscle proliferation in cell culture Although LDLs may mitogenic they more probably provide nutrients necessary for cell proliferation in terms of new membrane formation Human fibroblasts contain specific receptor sites for LDL and arterial smooth muscle cells are thought to have similar receptors that play a role in controlling the intracellular synthesis of cholesterol Recent investigations demonstrate that platelet alpha granules contain platelet derived growth factor (PDGF) a potent stimulator of smooth muscle cell proliferation[6] Since increased platelet activity in vitro has been reported in patients with familial hypercholesterolemia it is necessary to determine whether the decreased survival is a direct effect of increased cholesterol or lipoproteins upon the platelets or is a manifestation of increased platelet consumption by exposed subendothelial surfaces

Ross and Harker[66] performed matched cross over platelet survival experiments in normal lipidemic and hyperlipidemic monkeys and demonstrated that platelets from hyperlipidemic monkeys survived normally after infusion into normal lipidemic animals In contrast platelets from normal lipidemic animals infused into hyperlipidemic animals had a decreased survival time comparable with that of autologous platelets While such data do not rule out the possibility of a rapidly occurring lipid mediated effect on the membranes of transfused platelets the reduction in platelet survival is most consistent with increased platelet consumption on exposed subendothelial surfaces as observed in the desquamation associated with homocystinemia and in prostheses such as artificial valves or vessels Platelet derived growth factor (PDGF) in contrast to the situation with other polypeptide hormones is distinctive in that the predominant delivery system for PDGF is the platelet rather than the plasma PDGF is primarily carried through the circulation in the alpha granules of the platelet and while it is in this cryptic state it cannot stimulate cell replication Since platelets have an affinity for injured sites they provide a remarkably specific delivery system for this polypeptide hormone which initiates the replication of arterial smooth muscle cells in vitro and may do so in vivo

As a further support of the role of platelets in atherosclerosis it should be remembered that pigs with von Willebrand s disease have a defect in platelet adhesion Bowie and associates showed that such animals failed to develop the athero-sclerotic lesions that occur in control animals made hypercholesterolemic by a fatty diet. Thus a suspected fundamental response following some form of injury to the endothelium may be platelet mediated intimal smooth muscle proliferation In addition when vascular damage leads to platelet deposition in the endothelial wall liberation of the vasoconstrictor thromboxane A_2 occurs tending to propagate the platelet aggregation process and perhaps collaborating in the development of coronary spasm [71] Enzymatic formation of prostacycline is specifically inhibited in vitro by lipid peroxide such as 15 hydroperoxyarachidonic acid and inhibition of the formation of this thrombolytic agent by lipid peroxides may provide an explanation for the development of some thrombotic episodes A variety of studies have demonstrated the ability of catecholamines to enhance platelet stickiness and aggregation while other studies have demonstrated increased platelet aggregation and consumption under a variety of situations both emotional and physical broadly referred to as stress [73]

To summarize what is known and highly suspected about the hypothesized roles of the various risk factors in the atherogenic process

1 Hypertension increases local vascular trauma turbulence with its greatest hydrodynamic impact at branching sites of vascular origin and serves as an instrument for inducing mechanical trauma

might be called competitive arousal struggle for dominance and the expected psychomotor consequences of the fight or flight mechanism With regard to the previously mentioned animal studies concerning alterations in the environment it seems reasonable to suspect that environmental stress and sociocultural factors importantly influence the type of behavior observed Industrialized western societies have in common a depersonalized complexity and reward system for the effective competitor In general these societies tend to reward those who are time urgent and aggressive Thus in some ways there is a curious resemblance between Henry and Ely s studies of an agonistic society in mice and contemporary industrialized societies

We would contend that a social structure which positively reinforces competition aggression and time urgent performance would result in a perpetual dynamic struggle for status and dominance so characteristic of the Type A psychomotor behavioral pattern Such behavior reinforced and rewarded by agonistic societies is attended by all the previously discussed physiologic mechanisms implicated in the pathogenesis of coronary atherosclerosis These include large fluctuations in blood pressure excessive catecholamine and ACTH production enhanced lipid mobilization and increased platelet aggregation

Such observations do not deny the importance of innate physiologic reactivity nor should we minimize the important influence of heredity Nevertheless if we are to talk about risk factors as phenomena which may accelerate or foster the biologic time clock of a degenerative process the psychosocial and behavioral factors discussed provide a unifying link between epidemiologic and pathophysiologic mechanisms in the study of coronary atherosclerosis We still must elucidate the intrinsic processes whereby such factors lead to the onset of clinical coronary heart disease Yet when such fundamental mechanisms are understood it should not be too difficult to understand the role of emotion and the neuroendocrine system in fostering such processes

Hypertension

Hypertension affects approximately 35 million Americans and can be traced to an identifiable cause in less than 10% of the cases Despite the widespread popular conception that an inner feeling of nervous tension is in fact hypertension we know that objective evidence for such equivalency is nonexistent However, a sizeable and diverse number of scientific observations strongly suggest that psychosocial and behavioral factors participate in the pathogenesis of hypertension The ability of adverse psychosocial situations to evoke chronic hypertension was alluded to earlier in the work of Henry While the strength of evidence in the clinical arena is less than that for objective controlled animal experiments such psychosocial factors as socioeconomic level, crime rate residential change and overcrowding have been linked with hypertension

Harburg and colleagues[1] have shown that blacks living in areas of Detroit with low ecologic stress had less hypertension than their counterparts living in high stress areas Gampel and co workers[2] have reported that there was less hypertension among rural than among urban Zulus of the latter more of those who clung to traditional cultural practices and seemed unable to successfully adapt to the demands of urban living were hypertensive In general a remarkable contrast can be found between industrialized and primitive societies that demonstrates the relative absence of hypertension in the latter Yet immigrants from primitive societies to urban communities develop hypertension with equal or greater incidence facility and severity Apropos to these observations is the comment of Ostfeld and Shekelle[3] There has been an appreciable increase in uncertainty of human relations as man has gone from the relatively primitive and more rural to the urban and industrial Contemporary man in much of the world is faced every day with people and with situations about which there is uncertainty of outcome wherein appropriate behavior is not prescribed and validated by tradition where the possiblity of bodily or psychological harm exists where running or fighting is inappropriate and where mental vigilance is called for "[3]

In reality the agonistic society of Henry and Ely s animal experiments is tantamount to the society of urbanized industrialized man However just as different genetic strains of the same species manifest different temperaments and potential for developing hypertension it is likely that similar modifiers are operative in the clinical setting Whatever provocation or stress may emanate from a social environment genetic predisposition and cognitive integration are equally important factors in the equation resulting in hypertension The mosaic theory of pathophysiol

chological components such as anxiety depression psychosocial problems and physiological variations pathophysiological aging mechanisms and genetic susceptibility are not easily assessed Clearly the most diagnostic of the available tests in the assessment of Type A behavior is the structured interview of Friedman and Rosenman None however was considered satisfactory with regard to prognostic sensitivity specificity and selectivity in predicting the advent of coronary heart disease The panel did however recommend that the structured interview be considered the most suitable as a standard at this time The Type A behavior as evaluated by the structured interview is manifested by behavioral styles of loud explosive rapid and accelerated speech with short response latency hostility and a tendency toward verbal competition

Speed impatience hostility competitive drive and a sense of an effort oriented person caught up in a joyless struggle constitute the fully developed Type A behavior pattern Glass observations that the Type A personality is vulnerable to depression are in accord with the results of a study by Thomas Ross and Duszynski of physicians with myocardial infarcts who readily became depressed even as students and likewise with the results of a study by Bruhn and colleagues [a] of the coronary prone individual as an effort oriented person whose achievements give him little satisfaction

The mechanisms through which Type A behavior operates as a risk factor and by which it facilitates the progression of coronary heart disease remain conjectural a weakness shared with all risk factors until the pathogenesis of coronary atherosclerosis is fully understood However the prevalence of certain biochemical and physiological phenomena are highly associated with fully developed Type A behavior These include elevated serum cholesterol levels elevated pre and postprandial serum triglycerides enhanced platelet aggregation faster clotting time higher excretion of norepinephrine particularly when provoked by emotional challenge a higher average serum level of corticotropin a greater insulinemic response to glucose a decreased growth hormone response to arginine and greater lability and magnitude of blood pressure response under time demand tasks [7]

It is important to make a distinction between Type A behavior and the ill defined but constantly evolving concept of coronary prone behavior Individuals manifesting Type A behavior may survive unscathed into old age attending the funerals of their younger Type B counterparts Thus the association is incomplete It is obvious that genetic perceptive and other coping factors operate to counterbalance predisposing behavioral effects in many individuals and only certain components of Type A behavior correlate with coronary heart disease Furthermore the cognitive integrative aspects of behavior and their link to pathophysiologic responses remain largely unknown

If by behavior one means the actions or reactions of man or animals under specified circumstances a recent study by Dembroski and associates illustrates the distinction between behavior in coronary patients and in non coronary control patients During a structured interview and an American history quiz they noted an increase in systolic blood pressure during the history quiz in Type B coronary patients but not in Type B controls Indeed the greatest increment of blood pressure change in either Type A or B groups was evoked in Type B myocardial infarction patients during the American history quiz Such observations suggest that we must attempt to examine and integrate the multifaceted aspects of overt psychomotor behavior with those of cognition and physiologic behavior if we are to gain further understanding of how behavioral facets translate into coronary proneness

Yet if we return to what is known and suspected concerning the pathophysiology of the other risk factors it is obvious that each represents a single manifestation of a more complex underlying process What constitutes the fundamental pathophysiology remains conjectural but it is relatively certain that the orchestration of such factors occurs in a living emotional reacting organism attempting to adapt to its environment in the interest of maintaining its own integrity A variety of psychosocial and conditioning experiments in animals point clearly to mechanisms attending the development of accelerated atherosclerosis and the neuroendocrine system is undoubtedly of pivotal importance in orchestrating the pathophysiologic mechanisms culminating in atherosclerosis

Type A behavior is recognized by its psychomotor components which in the fully developed pattern are easily recognized as signs of what

dins, their intermediates and precursors. Cardiovascular actions and regulatory roles in normal and abnormal circulatory systems, Prog. Cardiovasc. Dis 21 405 1979

72. Haft J I., and Arkel, Y S Effect of emotional stress on platelet aggregation in humans, Chest 70 501 1976
73. Fleischman, A. L., Bierenbaum M L., and Stier A. Effect of stress due to anticipated minor surgery upon in vivo platelet aggregation in humans, J Human Stress 2 33 1976
74. Friedman M., and Rosenman R. H Association of a specific overt behavior pattern with increases in blood cholesterol blood clotting time incidence of arcus senilis and clinical coronary artery disease J A M A. 169 1286 1959
75. Coronary prone behavior and coronary heart disease A critical review Report of the Coronary Prone Behavior Review Panel submitted to the National Heart Lung and Blood Institute National Institutes of Health December 1978
76. Glass, D C Behavior Patterns, Stress and Coronary Disease Hillsdale N J 1977 Lawrence Erlbaum Associates.
77. Thomas, C B., Ross D C., and Duszynski, K. R. Youthful hypercholesterolemia its associated characteristics and role in premature myocardial infarction John Hopkins Med. J 136 193 1975
78. Bruhn J G., Paredes, A., Adsett C A., and Wolf S Psychological predictors of sudden death in myocardial infarction, J Psychosom Res. 18 187 1974
79. Dembroski, T M., MacDougall J M and Shields J L. Physiologic reaction to social challenge in persons evidencing the Type A coronary prone behavior pattern J Human Stress 3 2, 1977
80. Dembroski, T M., MacDougall J M., and Lushene R. Interpersonal interaction and cardiovascular response in type A subjects and coronary patients, J Human Stress 5 28 1979
81. Harburg, E., Schull W J Erfurt, J C et al. A family set method for estimating heredity and stress. I. A pilot survey of blood pressure among Negroes in high and low stress areas, Detroit, 1966-1967 J Chronic Dis. 23 [illegible] 1970
82. Gampel, B., Slome C., Scotch, N and Abramson, J H. Urbanization and hypertension among Zulu adults, J Chronic Dis. 15 67 1962.
83. Ostfeld A. M and Shekelle R. B Psychological variables and blood pressure in The Epidemiology of Hypertension eds. J Stamler R. Stamler and T N Pullman, New York, 1967 Grune & Stratton, Inc., pp [illegible]
84. Page I H. Pathogenesis of arterial hypertension [illegible] 140 451 1949
85. Alexander F Psychosomatic Medicine Its Principles and Applications, New York, 1950 W W Norton & Company Inc.
86. Esler M., Julius, S., Zweifler A., Randall O Harburg E, Gardiner H., and DeQuattro V.. Mild high-renin essential hypertension. Neurogenic human hypertension [illegible] Engl. J Med. 296 405 1977
87. Kalis, B L., Harris, R. E., Sokolow M and Carpenter L G Response to psychological stress in patients with essential hypertension, AM HEART J 53 572, 1957
88. Weiner H., Singer M T., and Reiser M. F Cardiovascular responses and their correlates. A study in healthy young adults and patients with peptic ulcer and hypertension Psychosom Med. 24 477 1962
89. Sapira J D., Scheib E. T Moriarty R., and Shapiro A.P Differences in perception between hypertensive and normotensive populations, Psychosom. Med. 33 [illegible] 1971
90. deChamplain J The sympathetic system in hypertension in Clinics in Endocrinology and Metabolism, volume 6 Catecholamines, ed. Landsberg, L., London, 1977 W B Saunders Company Ltd pp 633-6[illegible]

ogy proposed by Page[34] seems appropriate and useful From this vantage point the socioenvironmental association with hypertension seen in a variety of epidemiologic studies suggests that social or emotional stress may play a role in the pathogenesis of hypertension Controversies concerning the term environmental stress aside we find it more understandable and therefore more useful to view stress by its effect upon the organism in question, that effect being strain Therefore we know stress by the company it keeps namely strain It seems necessary for perceptive and cognitive processes to determine whether outside forces represent for that individual a strain inducing phenomenon There is no other apparent explanation for the old adage that beauty is in the eye of the beholder

Beyond considerations of environmental provocation psychological and behavioral aspects are also worthy of note Work by Alexander[35] suggests that the hypertensive personality may be described as an individual who frequently manifests inhibited and poorly expressed rage and anger It has been proposed that this inhibited rage or anger turned inward results in stimulation of the autonomic nervous system which causes the release of significant amounts of norepinephrine leading to acute and eventually chronic hypertension The influence of catecholamines upon renin release has already been mentioned and Esler and colleagues have reported that in psychometric testing patients with high renin hypertension exhibited suppressed hostility linked to increased sympathetic activity In these patients the hypertension was concluded to be neurogenic and possibly psychosomatic in origin Such individuals are described as withdrawn not easily communicative and tending to avoid confrontation with people even when rage is justified At times such individuals may seem obsequious in their efforts to avoid conflict in order to please those individuals with whom they are involved in interpersonal relationships

On the other hand it may be somewhat naive to postulate that personality patterns influence the autonomic nervous system and thus produce hypertension Others have suggested that this behavior may be a manifestation of an awareness by hypertensives of their hyperreactive cardiovascular system and the observed behavior represents attempts to withdraw from confrontation lest they evoke excessive and potentially harmful responses[37] • Work by some investigators suggests that hypertensive patients deny the difference between a neutral and an overtly confrontational movie drama as if in some manner they had managed to avoid perceiving what was an obvious confrontation[39]

Studies have indicated that 25% to 40% of patients with essential hypertension are characterized by higher basal circulating catecholamine levels and by higher sympathetic activity in response to postural changes[40] The identification of these patients as a separate entity is desirable since it is possible that the evolution of the hypertensive disease and response to therapy may differ in this group

Whether observations linking personality behavior and neuroendocrine mechanisms with hypertension constitute valid clues to the pathogenesis of essential hypertension or a protective response to genetic vulnerability or even a functional defect as a consequence of the disease process remains to be elucidated However a wide variety of experimental and clinical observations implicate psychosocial and behavioral factors in the phenomenon of essential hypertension The interaction between mind and environment engrafted upon a genetic substrate is a complex topic for study Yet the foregoing discussions of neuroendocrine mechanisms and consideration of the concept that essential hypertension represents specific disturbances or shifts in the bias of physiologic regulatory mechanisms is consistent with observed data in epidemiologic experimental and clinical data Since either adrenal medullary or adrenal cortical systems can lead to hypertension and are known to be activated by psychosocial stimuli with concomitant behavioral phenomena it is not too difficult to see that repeated exposure to such stimuli can lead to structural vascular thickening and mechanically increased resistance Whereas initially the imbalance is probably reversible chronically repeated and sustained arousals are likely to result in a permanent disregulatory state with fixed hypertension One cannot underestimate the importance of psychosocial and neuroendocrine elements early but it is likely that these become less significant in the later stages of hypertension

Summary

When taken together studies relating psychosocial and behavioral factors to cardiovascular disease phenomena provide justification for the conclusion that such factors are importantly

might be called competitive arousal struggle for dominance and the expected psychomotor consequences of the fight or flight mechanism With regard to the previously mentioned animal studies concerning alterations in the environment it seems reasonable to suspect that environmental stress and sociocultural factors importantly influence the type of behavior observed Industrialized western societies have in common a depersonalized complexity and reward system for the effective competitor In general these societies tend to reward those who are time urgent and aggressive Thus in some ways there is a curious resemblance between Henry and Ely s studies [9] of an agonistic society in mice and contemporary industrialized societies

We would contend that a social structure which positively reinforces competition aggression and time urgent performance would result in a perpetual dynamic struggle for status and dominance so characteristic of the Type A psychomotor behavioral pattern Such behavior reinforced and rewarded by agonistic societies is attended by all the previously discussed physiologic mechanisms implicated in the pathogenesis of coronary atherosclerosis These include large fluctuations in blood pressure excessive catecholamine and ACTH production enhanced lipid mobilization and increased platelet aggregation

Such observations do not deny the importance of innate physiologic reactivity nor should we minimize the important influence of heredity Nevertheless if we are to talk about risk factors as phenomena which may accelerate or foster the biologic time clock of a degenerative process the psychosocial and behavioral factors discussed provide a unifying link between epidemiologic and pathophysiologic mechanisms in the study of coronary atherosclerosis We still must elucidate the intrinsic processes whereby such factors lead to the onset of clinical coronary heart disease Yet when such fundamental mechanisms are understood it should not be too difficult to understand the role of emotion and the neuroendocrine system in fostering such processes

Hypertension

Hypertension affects approximately 35 million Americans and can be traced to an identifiable cause in less than 10% of the cases Despite the widespread popular conception that an inner feeling of nervous tension is in fact hypertension we know that objective evidence for such equivalency is nonexistent However, a sizeable and diverse number of scientific observations strongly suggest that psychosocial and behavioral factors participate in the pathogenesis of hypertension The ability of adverse psychosocial situations to evoke chronic hypertension was alluded to earlier in the work of Henry While the strength of evidence in the clinical arena is less than that for objective controlled animal experiments, such psychosocial factors as socioeconomic level, crime rate residential change and overcrowding have been linked with hypertension

Harburg and colleagues [1] have shown that blacks living in areas of Detroit with low ecologic stress had less hypertension than their counterparts living in high stress areas Gampel and co workers [2] have reported that there was less hypertension among rural than among urban Zulus of the latter more of those who clung to traditional cultural practices and seemed unable to successfully adapt to the demands of urban living were hypertensive In general, a remarkable contrast can be found between industrialized and primitive societies that demonstrates the relative absence of hypertension in the latter Yet migrants from primitive societies to urban communities develop hypertension with equal or greater incidence facility and severity Apropos to these observations is the comment of Ostfeld and Chakelle [3] There has been an appreciable increase in uncertainty of human relations as man has gone from the relatively primitive and more rural to the urban and industrial Contemporary man in much of the world is faced every day with people and with situations about which there is uncertainty of outcome wherein appropriate behavior is not prescribed and validated by tradition where the possiblity of bodily or psychological harm exists where running or fighting is inappropriate and where mental vigilance is called for [3]

In reality the agonistic society of Henry and Ely s animal experiments is tantamount to the society of urbanized industrialized man However just as different genetic strains of the same species manifest different temperaments and potential for developing hypertension it is likely that similar modifiers are operative in the clinical setting Whatever provocation or stress may emanate from a social environment genetic predisposition and cognitive integration are equally important factors in the equation resulting in hypertension The mosaic theory of pathophysiol-

Antihypertensive therapy New pharmacological approaches

Gordon S Stokes M D F R A C P
Helen F Oates B Sc (Hon I) Ph D
C Paul MacCarthy M B B Ch M R C P I
Sydney Australia

Over the last 30 years an increasing proportion of hypertensive subjects have come to be treated with antihypertensive drugs The first drugs used though life saving in their day were too toxic and were replaced by others which produced fewer side effects Knowledge of the sites and mechanisms of action of antihypertensive agents has greatly increased Newer agents have been developed for greater selectivity However there has not been a corresponding growth in the understanding of the pathogenesis of hypertension nor is it yet feasible in the clinic to analyze the mechanisms giving rise to hypertension in individual patients Indeed it has been claimed that the concept of prospectively individualizing antihypertensive therapy remains largely hypothetical These considerations may help to explain why despite a steady flow of interesting new antihypertensive substances from the pharmaceutical industry clinical trials have often failed to confirm that greater specificity in drug action achieves a better therapeutic result We appear to have reached a plateau in therapeutic efficacy It may then be asked does a precise knowledge of the specific sites and mechanisms of drug action really help in choosing treatment for the individual patient with high blood pressure? Further what justification exists for prescribing the more selective drugs?

We propose that understanding the action of an antihypertensive agent helps to predict and recognize its side effects to avoid adverse interactions with other drugs and to obtain additive hypotensive effects by combining it with drugs acting elsewhere Such information is integral to the design of systems of stepped care therapy through which individualization of treatment though empirical can proceed along rational lines In this review we will outline what is known about the modes of action the side effects and the applications of currently available antihypertensive drugs and will analyze their contributions to a system of stepped care therapy

From the Cardio-Renal Unit Medical Research Department Kanematsu Memorial Institute Sydney Hospital Sydney Australia
Received for publication Oct 15 1979
Reprint requests Dr Gordon S Stokes Cardio-Renal Unit Medical Research Dept Kanematsu Memorial Institute Sydney Hospital Sydney Australia 2000

I Mechanisms of action and interaction of antihypertensive drugs

Antihypertensive drugs fall into four main groups diuretics angiotensin inhibitors vascular smooth muscle relaxants and sympatholytic drugs The clinical relevance of the angiotensin inhibitors is yet to be clearly defined and they are restricted to investigational use at present

1 Diuretics These act principally by causing renal loss of sodium and water with reduction in intravascular volume and cardiac output In the early stage of diuretic therapy the hypotensive effect reflects mainly a fall in cardiac output[3] In the later stage secondary adjustments restore cardiac output but blood pressure control is maintained through peripheral vasodilatation Discussion of the differences between the diuretics in their renal tubular actions is beyond the scope of this paper but may be found in the review by Seely and Dirks[5]

2 Angiotensin inhibitors act by preventing the effects of the renin angiotensin system upon vascular smooth muscle and possibly upon the adrenal cortex kidney and brainstem Angioten

might be called competitive arousal struggle for dominance and the expected psychomotor consequences of the fight or flight mechanism With regard to the previously mentioned animal studies concerning alterations in the environment it seems reasonable to suspect that environmental stress and sociocultural factors importantly influence the type of behavior observed Industrialized western societies have in common a depersonalized complexity and reward system for the effective competitor In general these societies tend to reward those who are time urgent and aggressive Thus in some ways there is a curious resemblance between Henry and Ely s studies[9] of an agonistic society in mice and contemporary industrialized societies

We would contend that a social structure which positively reinforces competition aggression and time urgent performance would result in a perpetual dynamic struggle for status and dominance so characteristic of the Type A psychomotor behavioral pattern Such behavior reinforced and rewarded by agonistic societies is attended by all the previously discussed physiologic mechanisms implicated in the pathogenesis of coronary atherosclerosis These include large fluctuations in blood pressure excessive catecholamine and ACTH production enhanced lipid mobilization and increased platelet aggregation

Such observations do not deny the importance of innate physiologic reactivity nor should we minimize the important influence of heredity Nevertheless if we are to talk about risk factors as phenomena which may accelerate or foster the biologic time clock of a degenerative process the psychosocial and behavioral factors discussed provide a unifying link between epidemiologic and pathophysiologic mechanisms in the study of coronary atherosclerosis We still must elucidate the intrinsic processes whereby such factors lead to the onset of clinical coronary heart disease Yet when such fundamental mechanisms are understood it should not be too difficult to understand the role of emotion and the neuroendocrine system in fostering such processes

Hypertension

Hypertension affects approximately 35 million Americans and can be traced to an identifiable cause in less than 10 % of the cases Despite the widespread popular conception that an inner feeling of nervous tension is in fact hypertension we know that objective evidence for such equivalency is nonexistent However, a sizeable and diverse number of scientific observations strongly suggest that psychosocial and behavioral factors participate in the pathogenesis of hypertension. The ability of adverse psychosocial situations to evoke chronic hypertension was alluded to earlier in the work of Henry While the strength of evidence in the clinical arena is less than that for objective controlled animal experiments, such psychosocial factors as socioeconomic level, crime rate residential change, and overcrowding have been linked with hypertension

Harburg and colleagues[11] have shown that blacks living in areas of Detroit with low ecologic stress had less hypertension than their counterparts living in high stress areas. Gampel and co workers[12] have reported that there was less hypertension among rural than among urban Zulus, of the latter more of those who clung to traditional cultural practices and seemed unable to successfully adapt to the demands of urban living were hypertensive In general a remarkable contrast can be found between industrialized and primitive societies that demonstrates the relative absence of hypertension in the latter Yet immigrants from primitive societies to urban communities develop hypertension with equal or greater incidence facility and severity Apropos to these observations is the comment of Ostfeld and Shekelle[53] There has been an appreciable increase in uncertainty of human relations as man has gone from the relatively primitive and more rural to the urban and industrial. Contemporary man in much of the world is faced every day with people and with situations about which there is uncertainty of outcome wherein appropriate behavior is not prescribed and validated by tradition where the possibility of bodily or psychological harm exists where running or fighting is inappropriate and where mental vigilance is called for [53]

In reality the agonistic society of Henry and Ely s animal experiments[20] is tantamount to the society of urbanized industrialized man. However just as different genetic strains of the same species manifest different temperaments and potential for developing hypertension it is likely that similar modifiers are operative in the clinical setting Whatever provocation or stress may emanate from a social environment genetic predisposition and cognitive integration are equally important factors in the equation resulting in hypertension The mosaic theory of pathophysiol

ogy proposed by Page[84] seems appropriate and useful From this vantage point the socioenvironmental association with hypertension seen in a variety of epidemiologic studies suggests that social or emotional stress may play a role in the pathogenesis of hypertension Controversies concerning the term environmental stress aside we find it more understandable and therefore more useful to view stress by its effect upon the organ in question that effect being strain Therefore we know stress by the company it keeps namely strain It seems necessary for perceptive and cognitive processes to determine whether outside forces represent for that individual a strain inducing phenomenon There is no other apparent explanation for the old adage that beauty is in the eye of the beholder

Beyond considerations of environmental provocation psychological and behavioral aspects are also worthy of note Work by Alexander[85] suggests that the hypertensive personality may be described as an individual who frequently manifests inhibited and poorly expressed rage and anger It has been proposed that this inhibited rage or anger turned inward results in stimulation of the autonomic nervous system which causes the release of significant amounts of norepinephrine leading to acute and eventually chronic hypertension The influence of catecholamines upon renin release has already been mentioned and Esler and colleagues[8] have reported that in psychometric testing patients with high renin hypertension exhibited suppressed hostility linked to increased sympathetic activity In these patients the hypertension was concluded to be neurogenic and possibly psychosomatic in origin Such individuals are described as withdrawn not easily communicative and tending to avoid confrontation with people even when rage is justified At times such individuals may seem obsequious in their efforts to avoid conflict in order to please those individuals with whom they are involved in interpersonal relationships

On the other hand, it may be somewhat naive to postulate that personality patterns influence the autonomic nervous system and thus produce hypertension Others have suggested that this behavior may be a manifestation of an awareness by hypertensives of their hyperreactive cardiovascular system and the observed behavior represents attempts to withdraw from confrontation lest they evoke excessive and potentially harmful responses[8, 9] Work by some investigators suggests that hypertensive patients deny the difference between a neutral and an overtly confrontational movie drama as if in some manner they had managed to avoid perceiving what was an obvious confrontation[89]

Studies have indicated that 25% to 40% of patients with essential hypertension are characterized by higher basal circulating catecholamine levels and by higher sympathetic activity in response to postural changes[90] The identification of these patients as a separate entity is desirable since it is possible that the evolution of the hypertensive disease and response to therapy may differ in this group

Whether observations linking personality behavior and neuroendocrine mechanisms with hypertension constitute valid clues to the pathogenesis of essential hypertension or a protective response to genetic vulnerability or even a functional defect as a consequence of the disease process remains to be elucidated However a wide variety of experimental and clinical observations implicate psychosocial and behavioral factors in the phenomenon of essential hypertension The interaction between mind and environment engrafted upon a genetic substrate is a complex topic for study Yet the foregoing discussions of neuroendocrine mechanisms and consideration of the concept that essential hypertension represents specific disturbances or shifts in the bias of physiologic regulatory mechanisms is consistent with observed data in epidemiologic experimental and clinical data Since either adrenal medullary or adrenal cortical systems can lead to hypertension and are known to be activated by psychosocial stimuli with concomitant behavioral phenomena it is not too difficult to see that repeated exposure to such stimuli can lead to structural vascular thickening and mechanically increased resistance Whereas initially the imbalance is probably reversible chronically repeated and sustained arousals are likely to result in a permanent disregulatory state with fixed hypertension One cannot underestimate the importance of psychosocial and neuroendocrine elements early but it is likely that these become less significant in the later stages of hypertension

Summary

When taken together studies relating psychosocial and behavioral factors to cardiovascular disease phenomena provide justification for the conclusion that such factors are importantly

dins their intermediates and precursors. Cardiovascular actions and regulatory roles in normal and abnormal circulatory systems Prog Cardiovasc Dis 21 40, 1979

2. Haft J I and Arkel Y S Effect of emotional stress on platelet aggregation in humans Chest 70 501 1976

3 Fleischman A I, Bierenbaum M L and Stier A Effect of stress due to anticipated minor surgery upon in vivo platelet aggregation in humans J Human Stress 2 33 1976

4 Friedman M., and Rosenman R H Association of a specific overt behavior pattern with increases in blood cholesterol blood clotting time incidence of arcus senilis and clinical coronary artery disease J A M A 169 1286 1959

5 Coronary prone behavior and coronary heart disease A critical review Report of the Coronary Prone Behavior Review Panel submitted to the National Heart Lung and Blood Institute National Institutes of Health December 1978

6 Glass D C Behavior Patterns, Stress and Coronary Disease Hillsdale N J 1977 Lawrence Erlbaum Associates

7 Thomas C B Ross, D C and Duszynski, K R Youthful hypercholesterolemia its associated characteristics and role in premature myocardial infarction John Hopkins Med J 136 193 1975

8 Bruhn J G Paredes A. Adsett C A and Wolf S Psychological predictors of sudden death in myocardial infarction J Psychosom Res. 18 187 1974

9 Dembroski T M MacDougall J M and Shields J L. Physiologic reaction to social challenge in persons evidencing the Type A coronary prone behavior pattern J Human Stress 3 2 1977

0 Dembroski, T M MacDougall J M and Lushene R Interpersonal interaction and cardiovascular response in type A subjects and coronary patients J Human Stress 5 28 1979

81 Harburg E Schull W J Erfurt, J C et al A family set method for estimating heredity and stress. I. A pilot survey of blood pressure among Negroes in high and low stress areas, Detroit 1966-1967 J Chronic Dis 23 69 1970

82 Gampel B Slome C Scotch N and Abramson, J H. Urbanization and hypertension among Zulu adults, J Chronic Dis 15 67 1962.

83 Ostfeld A. M and Shekelle R. B Psychological variables and blood pressure *in* The Epidemiology of Hypertension eds. J Stamler R. Stamler and T N Pullman, New York, 1967 Grune & Stratton Inc pp 321 331

84 Page I H Pathogenesis of arterial hypertension, 140 451 1949

85 Alexander F Psychosomatic Medicine Its Principles and Applications, New York, 1950 W W Norton & Company Inc

86 Esler M., Julius, S Zweifler A Randall O Harburg E Gardiner H., and DeQuattro V., Mild high renin essential hypertension. Neurogenic human hypertension? N Engl. J Med 296 405 1977

87 Kalis, B L., Harris R E., Sokolow M and Carpenter L G Response to psychological stress in patients with essential hypertension Am Heart J 53 572, 1957

88 Weiner H Singer M T and Reiser M F Cardiovascular responses and their correlates. A study in healthy young adults and patients with peptic ulcer and hypertension Psychosom Med 24 477 1962.

89 Sapira J D Scheib E T., Moriarty R., and Shapiro A P Differences in perception between hypertensive and normotensive populations, Psychosom. Med. 33 23 1971

90 deChamplain J The sympathetic system in hypertension *in* Clinics in Endocrinology and Metabolism, volume 6 Catecholamines, ed Landsberg L., London 1977 W B Saunders Company Ltd pp 633-655

Scott, eds. The Physiology of Aggression and Defeat, New York 1971 Plenum Publishing Corp pp 265-290

Katz J L Weiner H Gallagher T F, and Hellman L Stress, distress and ego defenses Psychoendocrine response to impending breast tumor biopsy Arch Gen Psychiatry 23 131 142, 1970

Carroll B J Limbic system adrenal cortex regulation in depression and schizophrenia Psychosom Med 38 106 1976

Gunn C G Friedman M and Byers S O Effect of chronic hypothalamic stimulation upon cholesterol induced atherosclerosis in the rabbit J Clin Invest 39 1963, 1960

Friedman M Byers S O and Brown A E Plasma lipid responses of rats and rabbits to an auditory stimulus, Am J Physiol 212 1174 1967

Friedman M and Byers S O Effect of environmental influences on alimentary lipemia of the rat Am J Physiol 213 1359 1967

Friedman M Byers S O and Elek S R Neurogenic hypercholesterolemia II Relationship to endocrine function Am J Physiol 223 473 1972

Stout L C and Bohorquez F Significance of intimal arterial changes in non human vertebrates Symposium on Atherosclerosis ed M D Altschule Medical Clinics of North America Vol 58 Philadelphia 19 8 W B Saunders Company pp 245-255

Stout, L C Lemmon W B, Bohorquez F et al Increased aortic arteriosclerosis with chronic electric shock in miniature pigs (Abstract) Am J Pathol 70 55a 1973

Dembroski, T M, Weiss S M, Shields, J L Haynes, S G and Feinleib M eds Coronary Prone Behavior New York 1978 Springer Verlag

Lynch, J J Paskewitz D A Gimbel K S and Thomas S A Psychological aspects of cardiac arrhythmia AM HEART J 93 645 1977

Jenkins, C D Recent evidence supporting psychologic and social risk factors for coronary disease N Eng J Med 294 987 1033 1976

Dimsdale J E Emotional causes of sudden death Am J Psychiatry 134 1361 1977

Eliot, R. S Stress and the Major Cardiovascular Disorders Mount Kisco N Y 1979 Futura Publishing Company

1 Buell J C and Eliot R S Stress and cardiovascular disease Mod Concepts Cardiovasc Dis 48 19 1979

1 Eliot R S and Buell, J C Environmental and behavioral influences in the major cardiovascular disorders Proceedings of the Academy of Behavioral Medicine Research, Snowbird Utah June 3-6 1979 (In press)

5 Celsus A C DeMedicina Liber III 6 circa 30 AD Quoted by East C F T in The Story of Heart Disease London 1957 William Dawson and Company

5 Harvey W Quoted in Eastwood M R and Trevelyan H Stress and coronary heart disease J Psychosom Res 15 289 1971

7 Home E A short account of the author's life in A Treatise on the Blood Inflammation and Gun Shot Wounds, ed. Hunter J, Philadelphia 1796 T Bradford Publishers, P I

8 Cannon W B Voodoo death Psychosom Med 19 182 1957

9 Osler W Lectures on angina pectoris and allied states, N Y Med, J 64 177 1896

0 Reynolds, R C Community and occupational influences in stress at Cape Kennedy Relationships to heart disease in Stress and the Heart ed. R S Eliot Mt. Kisco N Y 1974 Futura Publishing Company pp 33-49

51 Warheit G J Occupation A key factor in stress at the Manned Space Center in Stress and the Heart ed R S Eliot Mt Kisco N Y 1974 Futura Publishing Company pp 51-65

52\. Eliot R S Clayton F C Pieper G M and Todd G L Influence of environmental stress on the pathogenesis of sudden cardiac death Fed Proc 36 1719 1977

53 Eliot R S Todd G L, Clayton F C, and Pieper G M Experimental catecholamine-induced acute myocardial necrosis in Advances in Cardiology volume 25 eds V Manninen and P I Halonen Basel, 1978 S Karger AG pp 107 118

54 Berglund, G Sannerstedt, R, and Andersson, O Coronary heart disease after treatment of hypertension Lancet 1 1 1978

55 Raab W Emotional and sensory stress factors in myocardial pathology AM HEART J 72 538 1966

56 Engel, G L Psychologic stress, vasodepressor (vasovagal) syncope and sudden death Ann Intern Med 89 403 1978

57 Lown B DeSilva R A, and Lenson R Roles of psychologic stress and autonomic nervous system changes in provocation of ventricular premature complexes Am J Cardiol 41 979 1978

58 Gelhorn E Principles of Autonomic Somatic Integrations Minneapolis, 1967 University of Minnesota Press

59 De Silva R A, and Lown B The role of the central nervous system in fatal arrhythmias, J S C Med Assoc 75 567 1979

60 Kristensen B O and Petersen G B Association between coronary heart disease and the C3 gene in essential hypertension Circulation 58 622 1978

61 Keys A, Aravanis C, Blackburn H W et al. Epidemiological studies related to coronary heart disease Characteristics of men aged 40-59 in seven countries, Acta Med Scand (Suppl 460) 1 1967

62 Andrus, S B Portman O W and Riopelle A J Comparative studies of spontaneous and experimental atherosclerosis in primates II Lesions in chimpanzees including myocardial infarction and cerebral aneurysms, Prog Biochem. Pharmacol. 4 393 1968

63 Friedman M Rosenman, R. H and Carroll, V Changes in the serum cholesterol and blood clotting time in men subjected to cyclic variation of occupational stress Circulation 17 852 1958

64 Nerem R. Social environment as a factor in diet induced aortic atherosclerosis in rabbits, Hugh Lofland Conference on Arterial Wall Metabolism May 1979 Boston Mass.

65 Astrup P, and Kjeldsen K Carbon monoxide smoking and atherosclerosis, Symposium on Atherosclerosis, ed M. D Altschule Medical Clinics of North America volume 58 Philadelphia 1974 W B Saunders Company pp 323-350

66 Ross, R, and Harker L Hyperlipidemia and atherosclerosis, Science 193 1094 1976

67 Friedman R J, Stemerman M B Spaet, T H, Moore S and Gauldie J The effect of thrombocytopenia on arteriosclerotic plaque formation (Abstract) Fed Proc 35 207 1976

68 Kaplan D R, Chao F C Stiles, C D, Antoniades, H N, and Scher C D Platelet alpha granules contain a growth factor for fibroblasts, Blood 53 1043 1979

69 Bowie E J W, Fuster V, Owen, C A and Brown A L Paper presented at the 5th Congress of the International Society on Thrombosis and Haemostasis Paris, 1975

70 Haft J I Role of blood platelets in coronary artery disease Am J Cardiol 43 1197 1979

71 Dusting, G J, Moncada S, and Vane J R Prostaglan

Table I Main classes and generic names of antihypertensive drugs in general use

A *Diuretics*			
(a) Thiazide and related diuretics	(b) *Loop diuretics*	(c) Urico uric	(d) K e nser rg
Chlorothiazide	Furosemide	Ticrynafen	Spironolactone
Cyclopenthiazide	Ethacrynic acid		Triamterene
Bendrofluazide	Bumetanide		Amiloride
Methyclothiazide			
Metolazone			
B *Angiotensin inhibitors*			
(a) Angiotensin antagonists	(b) Converting enzyme inhibitors		
C *Vascular smooth muscle relaxants*			
Hydralazine	Diazoxide	Nifedipine	
Minoxidil	Verapamil	*Sodium nitroprusside*	
D *Sympatholytic drugs*			
(a) Centrally acting	(b) Peripherally acting	(c) β adrenergic blockers (site of action unclear)	
Reserpine	† Guanethidine	Propranolol	
Methyldopa	† Bethanidin	Oxprenolol	
Clonidine	† Debrisoquine	Alprenolol	
Guanabenz	‡ Phentolamine	Pindolol	
Tiamenidine	‡ *Phenoxybenzamine*	*Sotalol*	
Guanfacine	‡ Prazosin	Timolol	
	‡ *Indoramin*	*Acebutolol*	
	§ Labetolol	*Metoprolol*	
		Atenolol	

Gangl on blocking drug exclud d
†Neuron blocking drugs
‡Alpha adrenergic c ptor bl cki g drugs
§Combined alpha nd beta adrenergi recepto blocking drug

sin antagonists competitively block the action of angiotensin II on its receptors whereas converting enzyme inhibitors interfere with the conversion of angiotensin I to angiotensin II Unfortunately controversy surrounds the mode of action of the potentially most useful member of this group the converting enzyme inhibitor captopril This drug the only angiotensin inhibitor yet developed which is effective by the oral route, also potentiates the kinin system and possibly produces its hypotensive action in part through this or other still undefined pharmacologic mechanisms Nevertheless a recent review of 19 hypertensive patients treated for periods of up to 6 months has shown that the blood pressure reduction produced by captopril was correlated both with the pretreatment plasma renin activity and with the suppression of urinary aldosterone excretion

3 Vascular smooth muscle relaxant drugs alter cellular calcium flux and cause direct vasodilatation[8] Their actions are independent of alpha and beta adrenoreceptors

4 Sympatholytic drugs interfere with neurohumoral transmission at various points in the sympathetic nervous system This the large group can be divided on a pharmacological b into many classes However from a therapeu viewpoint the simple classification shown in Table I will suffice

The ways in which the centrally acting cla lower blood pressure are still unclear but they have in common the ability to reduce central sympathetic outflow This may be demonstrated most graphically by showing the decreased rate of spontaneous firing of pre ganglionic sympathetic neurons after administration of the drug into the cerebral ventricular system[9] In the case of methyldopa clonidine and clonidine like drugs (guanabenz tiamenidine and guanfacine) the reduction of sympathetic traffic appears to result from an alpha adrenergic agonist effect operating on the central inhibitory pathways leading to the vasomotor center, although other central mecha nisms of action have been proposed for clo dine[10] Reserpine causes depletion of catechol amines from both central and sympathetic neu rons[1] The action of methyldopa is thought

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Julian Frieden

Antihypertensive therapy New pharmacological approaches

Gordon S Stokes M D F R A C P
Helen F Oates B Sc (Hon I) Ph D
E Paul MacCarthy M B B Ch. M R C P I
Sydney Australia

Over the last 30 years an increasing proportion of hypertensive subjects have come to be treated with antihypertensive drugs The first drugs used though life-saving in their day were too toxic and were replaced by others which produced fewer side effects Knowledge of the sites and mechanisms of action of antihypertensive agents has greatly increased Newer agents have been developed for greater selectivity However there has not been a corresponding growth in the understanding of the pathogenesis of hypertension nor is it yet feasible in the clinic to analyze the mechanisms giving rise to hypertension in individual patients Indeed it has been claimed that the concept of prospectively individualizing antihypertensive therapy remains largely hypothetical These considerations may help to explain why despite a steady flow of interesting new antihypertensive substances from the pharmaceutical industry clinical trials have often failed to confirm that greater specificity in drug action achieves a better therapeutic result We appear to have reached a plateau in therapeutic efficacy It may then be asked does a precise knowledge of the specific sites and mechanisms of drug action really help in choosing treatment for the individual patient with high blood pressure? Further what justification exists for prescribing the more selective drugs?

We propose that understanding the action of an antihypertensive agent helps to predict and recognize its side effects to avoid adverse interactions with other drugs and to obtain additive hypotensive effects by combining it with drugs acting elsewhere Such information is integral to the design of systems of stepped care therapy through which individualization of treatment though empirical can proceed along rational lines In this review we will outline what is known about the modes of action the side effects and the applications of currently available antihypertensive drugs and will analyze their contributions to a system of stepped care therapy

I Mechanisms of action and interaction of antihypertensive drugs

Antihypertensive drugs fall into four main groups diuretics angiotensin inhibitors vascular smooth muscle relaxants and sympatholytic drugs The clinical relevance of the angiotensin inhibitors is yet to be clearly defined and they are restricted to investigational use at present

1 Diuretics These act principally by causing renal loss of sodium and water with reduction in intravascular volume and cardiac output In the early stage of diuretic therapy the hypotensive effect reflects mainly a fall in cardiac output [3] In the later stage secondary adjustments restore cardiac output but blood pressure control is maintained through peripheral vasodilatation Discussion of the differences between the diuretics in their renal tubular actions is beyond the scope of this paper but may be found in the review by Seely and Dirks [5]

2 Angiotensin inhibitors act by preventing the effects of the renin angiotensin system upon vascular smooth muscle and possibly upon the adrenal cortex kidney and brainstem Angioten

From the Cardio-R n l U it M dic l Resear h Department K nematsu M morial Institut Sydn y Hosp t l Syd ey Aust lia
Rece ed f r publ at n Oct. 15 1979
Reprint requests Dr Gordon S Stokes, Card o-Renal U t Medical Research Dept. Ka m tsu M morial Inst tut S dn y Hospital, Sydney Australia 2000

0002-8 03/80/110/41+12$01.20/0 © 1980 The C V Mosby Co

Table II *Homeostatic reflexes opposing blood pressure control*

1	Baroreceptor reflexes
	(a) Alpha adrenoceptor mediated vasoconstriction
	(b) Beta adrenoceptor mediated cardiac stimulation
2	Renal retention of salt and water
3	Renin angiotensin system

been proposed [18] However agents recently developed for beta 1 receptor blocking selectivity (metoprolol, atenolol) have proved to be at least as effective in reducing blood pressure as the non selective beta 1 and beta 2 receptor antagonists Thus it has been possible to decrease some of the undesired effects of beta 2 receptor blockade without loss of antihypertensive efficacy

Proper application of drugs of the sympatholytic group may be of critical importance in the treatment of severe hypertension because they counteract the baroreceptor mediated homeostatic reflexes which combat the antihypertensive effect of the other groups of drugs (see Table II) While there are several types of drugs acting at different sites which can interrupt sympathetic neural traffic to the vascular alpha adrenoreceptors the only antihypertensive agents which block the cardiac limb of the baroreceptor reflex are the beta adrenergic blockers It should be noted that they serve this important function in addition to exerting a hypotensive effect of their own Agents which diminish reflex cardioacceleration in less specific ways include clonidine (by central vagotonic and peripheral pre synaptic alpha receptor agonist interactions) and indoramin (by direct negative chronotropic effect)

A second homeostatic function that may interfere with blood pressure control is the renal retention of salt and water which occurs whenever kidney perfusion pressure drops This mechanism operates tending to restore the blood pressure to a high level when potent smooth muscle relaxant or sympatholytic drugs are used without adequate diuretic therapy The term false tolerance has been coined to emphasize the subtle nature of this problem which can exist in the absence of demonstrable edema To overcome such tolerance it may be necessary to use large doses of loop diuretics especially in patients with renal impairment

Another renal mechanism which can override the effects of antihypertensive agents is activation of the renin angiotensin system Increased circulating levels of renin and angiotensin together with an increased hypotensive response to angiotensin inhibitors are found during treatment with diuretics or smooth muscle relaxant drugs Conversely maintenance therapy with beta blockers reduces plasma renin activity to an extent determined mainly by the intrinsic sympathomimetic activity of the particular beta blocker used [1] and the influence of concomitant therapy In general the centrally acting sympatholytic drugs also decrease renin release where the peripherally acting class have a variable effect

To summarize the primary action of hypotensive drugs can be opposed by homeostatic reflexes listed in Table II Failure to respond to therapy may reflect the influence of one or more of these It is often possible to recognize the particular mechanism operative in an individual patient For example during treatment with a potent vasodilator agent the occurrence of edema weight gain or an increase in measured blood volume would point to the need for additional diuretic therapy whereas the presence of tachycardia and a high cardiac output state might call for the addition of a beta blocker to the therapeutic regimen

II Side effects Relevance to the application of particular drugs

A thorough knowledge of the side effects encountered with various antihypertensive drugs is essential for choosing the most suitable agent for each individual patient Side effects which can be anticipated and which may influence such choice are discussed below

A Diuretics

1 *Hypovolemia* A fall in blood volume may occur immediately after the introduction of diuretic therapy or with the intermittent use of a diuretic Because of the associated hazard of hypotension and blood hyperviscosity, a risk of precipitating cerebral ischemia exists in patients with cerebrovascular disease Thus the potent diuretics such as furosemide should rarely be used in elderly subjects and diuretic therapy avoided altogether in patients with transient ischemic attacks

2 *Hyperuricemia* Most diuretics tend to raise serum uric acid concentration probably of an increased passive reabsorption of urate

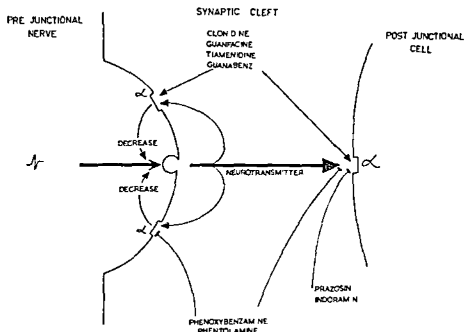


Fig 1 Actions of some antihypertensive agents on the alpha adrenergic receptors of the peripheral neuro-effector junction. → agonist effect ⊣ receptor blockade

depend on its active metabolites including alpha methylnorepinephrine which has a potent alpha agonist effect centrally but little peripheral effect Clonidine and its congeners have been shown to exert a potent agonist effect at the pre-synaptic alpha receptors of the sympathetic neuroeffector junction (see Fig 1) This property which causes a diminished release of neurotransmitter may contribute to the decrease in circulating catecholamines observed in patients treated with clonidine[13] or guanfacine[1] These agents also have a relatively weak peripheral post junctional alpha agonist effect which may result in an initial pressor response following their intravenous administration[1]

Those antihypertensive drugs which are known to have a predominantly peripheral site of action include the adrenergic neuron blocking agents and the alpha adrenergic receptor blockers (Table I) The ganglion blockers which interfere with parasympathetic as well as sympathetic pathways are now of historical interest only and have no part in the present-day treatment of hypertensive cardiovascular disease (although they still have a limited role in blood pressure control during anesthesia and in the treatment of aortic dissection e g trimethaphan) The adrenergic neuron blockers are taken up into the nerve ending by uptake the mechanism responsible for re uptake of neurotransmitter norepinephrine They displace the neurotransmitter in storage granules and also interfere directly with the coupling of nerve impulses to exocytotic release Alpha adrenergic receptor blockers lower blood pressure by preventing the agonist effect of neurotransmitter upon the post junctional alpha receptors at the sympathetic myoneural junctions of vascular smooth muscle (Fig 1) They may be classed as relatively selective (e g prazosin) or non selective (e g phenoxybenzamine) depending upon the degree to which the pre junctional alpha receptors are also blocked It has been suggested that pre junctional alpha adrenergic blockade which interferes with the negative feedback control of neurotransmitter release is disadvantageous and may account for the greater problems encountered with phenoxybenzamine in clinical practice than with prazosin[6] Labetalol a new antihypertensive agent with both alpha and beta adrenergic receptor blocking actions is more potent at beta receptors than at alpha receptors in man but it is not known which of these effects is of the greater importance in reducing blood pressure during chronic oral administration[1]

It has not been established how beta adrenoceptor blocking drugs lower blood pressure Various central and peripheral sites of action have

severe fluid retention[41,43] Pericardial effusion may occur without generalized edema[44] Hypertrichosis occurs in both sexes and the growth of facial hair commonly causes distress in women However calcium thioglycolate depilatory cream is effective in removing unwanted facial hair and causes little or no skin irritation thus allowing continuation of minoxidil therapy in women with hypertension resistant to other agents[45]

DIAZOXIDE Diazoxide has had its widest use in hypertension as an injectable solution given intravenously in a dose of 150 to 300 mg for the control of hypertensive crises A rapid fall in blood pressure tachycardia transient hyperglycemia and stimulation of renin release occur after injection[46] The latter effect has proved useful in diagnosing renovascular hypertension[4] Because it causes reflex tachycardia and increases cardiac output diazoxide should not be used to treat the severe hypertension associated with aortic dissection[48] The chronic administration of diazoxide by mouth although effective in controlling severe hypertension associated with renal failure is diabetogenic in about two thirds of subjects and may induce extrapyramidal symptoms[50]

VERAPAMIL Verapamil has received much more attention as an antianginal and antiarrhythmic compound than as an antihypertensive agent However its potent smooth muscle relaxant effect produces a fall in blood pressure[51] when the drug is administered orally or intravenously Constipation due to the relaxation of visceral smooth muscle is common[51] Since verapamil impairs atrioventricular conduction and myocardial contractility it should not be given to patients with heart block or cardiac failure nor should it be used in combination with beta adrenergic blocking drugs[52]

NIFEDIPINE This new vasodilator which was originally proposed for use in coronary vascular disease has a potent hypotensive action which lasts for 6 to 8 hours after oral or sublingual administration of a 20 mg dose[53] Side effects reported with its use include sensations of heat in the face and limbs and ankle edema Compared to verapamil nifedipine has a much less pronounced effect on the heart and may be used in combination with a beta blocking agent

SODIUM NITROPRUSSIDE Infusion of nitroprusside is an alternative to the use of diazoxide infusion in hypertensive crises Constant monitoring of blood pressure and plasma thiocyanate concentration is required to maintain blood pressure control and to prevent toxic encephalopathy[55] These objectives can be facilitated by the use of a microprocessor to control the rate of infusion[6]

D Sympatholytic drugs

a Centrally acting sympatholytic agents

1 SIDE EFFECTS RELATED TO CENTRAL DEPRESSANT ACTIVITY AND INTERACTIONS WITH PSYCHOTROPIC THERAPY All centrally acting antihypertensive drugs may cause significant daytime sedation which often improves spontaneously as therapy continues Those in widespread clinical use (reserpine methyldopa and clonidine) have each been associated with an appreciable incidence of severe depression Tricyclic antidepressant drugs may interfere with the antihypertensive actions of clonidine[5,58] or methyldopa[?] probably due to interactions at the central alpha adrenoreceptors in the brainstem. Unfavorable interactions may also occur between monoamine oxidase inhibitors and methyldopa. In view of the problems which can arise during the management of depressive patients receiving centrally acting antihypertensive agents they should not be prescribed for patients with a previous history of endogenous depression except in the exigency of known resistance to peripherally acting antihypertensive agents

2 WITHDRAWAL REACTIONS In patients treated with clonidine for severe hypertension abrupt withdrawal of this agent can provoke a syndrome characterized by acute hypertension tachycardia and other features of sympathetic discharge[59,6] Similar reactions have been noted after acute withdrawal of methyldopa guanabenz[64] and guanfacine[6] Considerable disagreement exists however concerning the incidence magnitude and clinical importance of true overshoot hypertension during withdrawal reactions There have been numerous case reports of severe and occasionally disastrous hypertensive crises after stopping clonidine and three groups have reported features of sympathetic overactivity with or without overshoot hypertension even after controlled withdrawal of the drug[60-62] Conversely others have found no evidence of sympathetic overactivity after withdrawal of the drug apart from raised urinary norepinephrine excretion[66] All these studies have been criticized on various grounds including lack of pretreatment blood pressure data and insufficiently close monitoring during the withdrawal phase The obvi...

the kidney accompanying compensatory shifts of proximal tubular fluid. In the case of ticrynafen this tendency is countered by specific inhibition of the re absorption of both filtered and secreted urate.[3] Clinical gout is precipitated in only a small proportion of patients who develop hyperuricemia as a result of treatment with a diuretic. In such individuals or in those who present with a history of gout of hyperuricemia a number of therapeutic strategies are available: a. Avoid the use of diuretics completely. b. Use ticrynafen. c. Use a diuretic plus probenecid (which inhibits renal tubular reabsorption of urate). d. Use a diuretic plus allopurinol, which inhibits the production of uric acid. If there is evidence of increased uric acid turnover, options (a) and (d) are preferable to (b) and (c), both of which promote uricosuria and can cause crystalluria.

3. *Changes in serum potassium levels.* All diuretics except those of the potassium conserving class (Table I) increase distal tubular potassium secretion and can lead to an appreciable fall in serum potassium concentration. This may have serious consequences in patients receiving digitalis or in those with primary aldosteronism, liver disease or pre existing potassium depletion. However diuretic induced hypokalemia rarely produces problems in patients with uncomplicated hypertension. Potassium conserving diuretics tend to produce hyperkalemia when given to patients with diabetes mellitus[28] or impaired renal function. Means of potassium supplementation and their relative efficacy and safety have been reviewed recently.[29]

4. *Carbohydrate intolerance.* Thiazide diuretics may cause a rise in blood sugar in diabetic patients[3] and may occasionally induce hyperglycemia and glycosuria in previously normal people.[3] Carbohydrate intolerance has also been reported with the use of loop diuretics.[3] The mechanism is not wholly understood[31] but there is evidence for both impaired pancreatic insulin release and defective glucose utilization by peripheral tissues. Thus a relative contraindication to diuretic therapy exists in patients with diabetes mellitus or known carbohydrate intolerance. This however should not countermand the use of diuretics in such subjects when their hypertension is resistant to other therapy or is complicated by fluid retention.

5. *Hypercalcemia.* Chronic administration of thiazide and related diuretics reduces calcium excretion by a mechanism analogous to that which pertains to urate.[3] A rise in serum calcium may result. This is usually minor but could be deleterious in patients with pre existing hypercalcemia due to metabolic disorders such as hyperparathyroidism.

B. Angiotensin inhibitors. Administration of the oral converting enzyme inhibitor captopril has induced febrile reactions,[7] rashes,[7] loss of taste sensation,[3] and reversible renal failure.[36] Intravenous administration of the angiotensin analog saralasin acetate has been associated with pheochromocytoma crisis occurring during the infusion and rebound hypertension with encephalopathy occurring one to three hours after stopping the infusion.[3] In general angiotensin inhibitors may produce severe depressor responses in conditions of strong angiotensin II dependency such as extreme sodium depletion, renovascular hypertension and intercurrent therapy with diuretic or vasodilator drugs.[39]

C. Vascular smooth muscle relaxants

1. *Side effects common to all smooth muscle relaxant drugs.* The symptoms of a hyperkinetic circulatory state (flushing, headache, and pounding in the ears or chest) may be observed with any drug which produces vasodilatation by a direct action on arteriolar smooth muscle. Tachycardia and fluid retention resulting from unopposed homeostatic adjustments (already outlined) are also common to all drugs of this group. All these symptoms may be countered by the adjunctive use of sympatholytic or diuretic agents, this being essential with the more potent drugs of the group such as minoxidil.

2. *Side effects peculiar to particular smooth muscle relaxant drugs.*

HYDRALAZINE. The most important side effect of hydralazine is the development of a syndrome resembling systemic lupus erythematosus. The drug is best avoided in patients with a family history of lupus and dosage should be restricted to a ceiling of 200 mg per day in known slow acetylators or in subjects with renal impairment. Other side effects specific to hydralazine have been reviewed by Alarcon Segovia and associates.

MINOXIDIL. This drug, the most potent of the orally active peripheral vasodilators, is potentially life saving for refractory hypertension coupled with progressive renal impairment but may cause

Table III Some contraindications to the use of certain drugs in hypertension

Condition	Drugs contraindicated
Gout Hyperuricemia Hypokalemia	Thiazide diuretics Loop diuretics
Hypercalcemia	Thiazide diuretics
Depression	Reserpine methyldopa Clonidine
Poor drug compliance	Clonidine
Transient ischemic attacks Old age	Potent diuretics Adrenergic neuron blockers Alpha adrenergic blockers
Treatment with tricyclic substances	Adrenergic neuron blockers Clonidine methyldopa
Angina pectoris Tachycardia	Smooth muscle relaxants Alpha adrenergic blockers
Cardiac failure Bradyarrhythmia A V block	Beta adrenergic blockers Verapamil
Asthma Insomnia	Beta adrenergic blockers
Raynaud s syndrome Calf Claudication	Non selective beta blockers

Except in the presence of beta adrenergic blockade

lower in incidence with beta 1 selective blockers than with those of indiscriminate beta 1 and beta 2 affinity However increased selectivity has resulted in limited gains because receptor selectivity is relative and not absolute and also because most organs appear to have populations of both beta 1 and beta 2 receptors despite a dominance of one type or the other Presumably the cardioselective drugs should have less tendency to produce bronchospasm or exacerbate symptoms of peripheral vascular disease However severe asthmatic reactions and Raynaud s phenomenon have been reported with the use of these selective agents All beta blockers should be avoided in asthmatic patients or in subjects who give a history of persistent wheeze during respiratory infections and similarly in patients with peripheral gangrene or other evidence of severe vasospasm Beta blockers are not contraindicated in hypertensive diabetic subjects except perhaps those whose control is brittle or those prone to frequent hypoglycemic reactions Beta 1 selective blockers are preferable for use in diabetic patients[80] The question of whether beta 1 selectivity improves diastolic blood pressure control

Table IV Some indications for the use of [illegible] drugs in hypertension

Condition	Drugs ind[illegible]
Cardiac failure Edema	Diuretics (any)
Hyperuricemia	Ticrynafen
Hypokalemia	K -conserving diuretics
Migraine	Clonidine Beta-adrenergic blockers
Angina Palpitations Ectopic beats Arrhythmias (not all)	Beta adrenergic blockers Verapamil
Recent myocardial infarction	Beta adrenergic blockers
Essential tremor	Propranolol
Severe cardiac failure	Prazosin Hydralazine Sodium nitroprusside Nifedipine

during stress is unresolved Although exog[illegible] epinephrine produces less rise in diastolic pres[illegible] during beta 1 blockade than during non select[illegible] beta blockade this phenomenon does not nece[illegible] sarily hold for situations of endogenous catech[illegible] amine release from the adrenal medulla or [illegible] pathetic nerve terminals[a]

III A system of stepped-care therapy

The questions to be considered in selecting [illegible] treatment for a given patient with hyperten[illegible] are

1 What characteristics of the patient cons[illegible] tute indications or contraindications for the us[illegible] of particular drugs?

2 Having decided which drugs suit the patie[illegible] what options exist for their use in appropria[illegible] combinations if combined therapy proves nece[illegible] sary to control the hypertension?

The first of these decisions involves pati[illegible] drug matching while the second involves th[illegible] matching of drug to drug in combinations wh[illegible] achieve additive hypotensive effects but mi[illegible] mize side effects Contraindications to spec[illegible] drugs and classes of drugs have been discussed and some of the more important examples [illegible] listed in Table III Certain indications for partic[illegible] ular drugs are given in Table IV

These considerations form a background [illegible]

difficulties in carrying out and interpreting appropriate experiments in hypertensive patients has pointed to the need for controlled studies in normotensive subjects and in experimental animals We have demonstrated significant overshoots in blood pressure and heart rate 16 to 24 hours after even single doses of clonidine or guanfacine in normotensive rats [7, 68] Another group has confirmed these findings although they failed to demonstrate overshoot in hypertensive rats [9]

It is the authors opinion that the hazards of clonidine withdrawal are real enough to warrant *avoiding this drug in patients who have a history* of poor compliance with drug therapy If chronic oral medication with clonidine is interrupted by acute gastrointestinal disorders or the need for general anesthesia therapy may be continued by the intramuscular route [7]

3 OTHER RELEVANT SIDE EFFECTS OF CENTRALLY ACTING ANTIHYPERTENSIVE AGENTS Drugs in this class may occasionally cause sexual dysfunction in males and so threaten compliance Since bowel disturbances may result from treatment with methyldopa or clonidine, it is preferable to avoid using these agents in patients with enterocolitis Reserpine especially when given in large doses may aggravate peptic ulcer disease Postural hypotension occurs infrequently with both methyldopa and clonidine but is more prominent with guanabenz which has a subsidiary peripheral adrenergic neuron blocking effect [7]

b *Peripherally acting sympatholytic agents*

1 SIDE EFFECTS OF NEURON BLOCKING DRUGS The side effects of this class which is long established in clinical therapy are well known and will not be detailed here The most important are postural hypotension diarrhea and interruption of the ejaculation reflex The antihypertensive action of neuron blockers is severely impaired by tricyclic antidepressant therapy [72] probably through competition for the neuronal uptake process

2 SIDE EFFECTS OF ALPHA ADRENERGIC RECEPTOR BLOCKING DRUGS Postural hypotension has been the most frequent and troublesome side effect with alpha adrenoceptor antagonists Hence it is inadvisable to use these drugs in the elderly or in subjects with known cerebrovascular or coronary insufficiency Particularly severe reactions have been reported after the initial dose of prazosin *or as a response to dosage increments* of this agent This first dose phenomenon is aggravated by prior sodium depletion[7] or by the presence of renal failure [4] It has been attributed to selective blockade of visceral sympathetic activity [73] but usually subsides despite continued therapy The problem is minimized by starting with a small dose in the evening [16] However postural hypotension and tachycardia persist during chronic therapy in a small proportion of patients and may necessitate withdrawal of the drug [1] Postural hypotension necessitated withdrawal of labetalol in three of 16 patients in one series treated with this combined alpha and *beta receptor blocking drug and has been a* prominent side effect in other recent trials with labetalol Failure of ejaculation occurs occasionally with labetalol but has not been definitely associated with prazosin or indoramin The use of indoramin even in low doses as part of a multiple drug regimen is limited by its central depressant action The other members of this class of drugs uncommonly cause central side effects and their acceptance by patients has been generally good except in the case of phenoxybenzamine [8]

3 SIDE EFFECTS OF BETA ADRENERGIC RECEPTOR BLOCKING DRUGS We will not attempt to give a comprehensive description of the side effects of this class which have been well reviewed elsewhere However certain guidelines may be helpful in selecting therapy

(i) The side effects of beta blockers can be readily predicted for the most part on the basis of their interference with beta receptor mediated sympathetic transmission to the heart bronchi and peripheral blood vessels The central nervous and metabolic effects of these drugs are less well understood

(ii) Since these agents interrupt sympathetic drive to the heart they should not be used in patients with heart failure bradyarrhythmias or atrioventricular conduction block

(iii) All drugs of this class reduce maximal exercise performance and tend to induce mild lassitude These effects are a consequence mainly of cardiac beta adrenergic blockade although peripheral vasoconstriction mediated by beta 2 receptor antagonism and central nervous depression may be contributory Beta blockers may prove unacceptable to patients who engage in competitive sports

(iv) Most other side effects including bronchospasm peripheral vasospasm and potentiation of *hypoglycemia in diabetic subjects* appear to

zine Thus if the addition of relatively small doses of either prazosin or hydralazine fails to achieve blood pressure control it may be necessary to increase the dose of methyldopa debrisoquine or clonidine above the levels indicated at Step 2

A further alternative at Step 3 is to substitute labetalol a combined alpha and beta adrenergic blocking drug for the beta blocker previously administered

Step 4 This step should be required only in the most resistant cases of severe chronic hypertension associated with evidence of progressive retinal renal or cardiac damage Two new elements are added (1) minoxidil a potent but potentially toxic smooth muscle relaxant drug the use of which is restricted by governmental regulation in most countries (as is that of oral diazoxide which is more toxic and probably not as frequently effective) (2) a dose finding escalation of diuretic therapy with furosemide bumetanide or ethacrynic acid The initial dose of minoxidil should be 2.5 mg twice a day increasing by increments of 2 5 mg twice a day to a maximum of 40 mg /day Beta blocker therapy is a prerequisite in order to counteract reflex tachycardia Doses of loop diuretic well beyond the conventional may be required to overcome the tendency to salt and water retention associated with hypertensive nephrosclerosis and minoxidil therapy, in the case of furosemide up to 500 mg twice a day may be required

Conclusions

The deployment of the newer more selective drugs for the treatment of hypertension can be analyzed from several points of view Ideally these drugs should be applied specifically in each case to correct the perturbation inducing hypertension Because the pathogenesis of most forms of hypertension is not clearly understood such a mechanistic approach is rarely possible at present However understanding the mode of action and the side effects of an antihypertensive drug does allow to a limited extent appropriate matching between drug and patient Even more importantly it allows the drug to be fitted into a system of stepped care therapy in which antihypertensive agents are combined for synergistic effects These effects depend upon the correction by one drug of the homeostatic reflexes activated by another and allow the toxicity produced by single agents in high dosage to be avoided

REFERENCES

1 Birkenhager W H and Schalekamp M A D H Control mechanisms in essential hypertension, Amsterdam 19[illegible] Elsevier p 168

2 Gross F *in* Antihypertensive Agents, Handbook of Experimental Pharmacology XXXIX, F Gross, ed, Berlin 1977 Springer Verlag, p 2

3 Frohlich E D Schnaper H W Wilson, I M and [illegible] E. D Hemodynamic alterations in hypertensive patients due to chlorothiazide N Engl. J Med. 262 [illegible]

4 de Carvalho J G R Dunn F G Lohmoller G and Frohlich E D Hemodynamic correlates of prolonged thiazide therapy comparison of responders and nonresponders Clin Pharmacol. Ther 22 [illegible] 19[illegible]

5 Seely J F., and Dirks J H Site of action of diuretic drugs Kidney Int 11 1 1977

6 Gavras H., Brunner H R., Turini, G A Kershaw G R, Tifft C P Cuttelod S Gavras, I Vukovich, R A, and McKinstry D N Antihypertensive effect of the oral angiotensin converting-enzyme inhibitor SQ 14225 in man N Engl J Med 298 991 19[illegible]8

7 Case D B Atlas S A., Laragh J H Sealey J E Sullivan P A and McKinstry D N Clinical experience with blockade of the renin angiotensin aldosterone system by an oral converting-enzyme inhibitor (SQ 14225 Captopril) in hypertensive patients, Progr Cardiovasc Dis 21 195 19[illegible]8

8 Lowenthal D T Clinical pharmacology of vasodilators N Y State J Med 79 66 1979

9 Waite R Inhibition of sympathetic nerve activity resulting from central alpha adrenoreceptor stimulation *in* Recent Advances in Hypertension P Milliez and M Safar ed Reims, 19[illegible]5 Boehringer Ingelheim p [illegible]

10 Franz D N Hare B D., and Neumayr R J Depression of sympathetic preganglionic neurons by clonidine evidence for stimulation of 5 HT receptors, Clin Exp Hypertension 1 115 19[illegible]8

11 Rand M J and Jurevics, H The pharmacology of rauwolfia alkaloids *in* Antihypertensive Agents, Handbook of Experimental Pharmacology XXXIX F Gross ed., Berlin 19[illegible] Springer Verlag p [illegible]

1[illegible] Kersting F Reid J L and Dollery C T Site of action of methyldopa in lowering the blood pressure in [illegible] Clin Exp Pharmacol. Physiol. Suppl 4 11 19[illegible]

13 Wing L M H Reid J L., Hamilton C A., Sever P Davies D S and Dollery C T Effects of clonidine on biochemical indices of sympathetic function and plasma renin activity in normotensive man Clin Sci. Mol. Med 53 45 197[illegible]

14 Zamboulis C Hamilton C A and Reid J L [illegible] 141 a centrally acting antihypertensive drug Effects on blood pressure and plasma and urinary noradrenaline in essential hypertension Proceedings of the 5th Scientific Meeting of the International Society of Hypertension Paris, 19[illegible]8 Abstracts p 304

15 Oates H F Stoker L M and Stokes G S In[illegible] tions between prazosin clonidine and direct vasodilators in the anaesthetized rat Clin Exp Pharmacol. Physiol 5 85 19[illegible]8

16 Stokes G S and Oates H. F Prazosin new alpha adrenergic blocking agent in treatment of hypertension Cardiovasc Med 3 41 19[illegible]8

17 Brogden R N Heel R C Speight T M and Avery G S Labetalol a review of its pharmacology and therapeutic use in hypertension Drugs 15 [illegible] 19[illegible]

18 Amer M S Mechanism of action of [illegible] hypertension Biochem Pharmacol 26 1[illegible] 19[illegible]

19 Finnerty F A Relationship of extracellular fluid volume to the development of drug resistance in the hypertensive patient AM HEART J 81 563 19[illegible]

guide the choice of options from the following stepped-care system which is summarized in Table V.

Steps 1 and 2 A thiazide diuretic remains the best choice for treating most mild cases of hypertension and as the initial component of stepped care therapy. More potent diuretics may be required for patients with hypertension and renal impairment or congestive heart failure. Until the role of ticrynafen in treating hyperuricemic hypertensive subjects has been established it is probably wisest to withhold diuretic treatment in patients with gout or hyperuricemia and to rely on the use of Step 2 agents.

The reasons for selecting a beta blocker above the alternatives given in Step 2 are twofold. First the incorporation of agents at Steps 3 and 4 is facilitated by prior beta blockade. Second the symptoms encountered with beta blocker therapy are usually mild and show little relationship to dose within the conventional therapeutic range (e.g., for propranolol 20 to 480 mg/day). Thus once therapy with a small dose is shown to be well tolerated dosage may be escalated with little fear of provoking new side effects. In mild to moderate hypertension adequate blood pressure control may be obtained by giving medication once per day. In severe cases it should be given twice per day except in the case of atenolol which has a longer duration of action.[3] Until more toxicological data have accumulated to show that beta 1 blockers are as safe as the established agents of the non selective type they should not necessarily be regarded as having superseded the latter. However as already outlined they are preferred in hypertensive subjects with diabetes or peripheral vasospasm. The conventional dose range for metoprolol is from 50 to 400 mg/day and for atenolol it is from 50 to 200 mg/day. Since the dose-response curve for atenolol flattens above 200 mg/day doses higher than this are not recommended.[3]

In patients with heart failure asthma or other contraindications to beta blockers there is a wide choice of alternatives including the three shown in Table V. We do not recommend using any of these agents in maximal dosages as it is usually better to go to Step 3 instead adding an additional agent. Thus the dosage ceiling recommended for methyldopa at Step 2 is about 1 gram/day for appreciable central depressant symptoms are commonly encountered with higher doses. The

Table V A stepped-care system of antihypertensive drug treatment

Step 1.	Diuretic		
Step 2	Diuretic + β blocker		
	Or Methyldopa	}	Low Dose
	Or Debrisoquine	}	Low Dose
	Or Clonidine	}	Low Dose
Step 3	Diuretic + β blocker + prazosin		
	Or other Or Hydralazine		
Step 4.	Loop diuretic + β blocker + minoxidil		

ceiling suggested at Step 2 for clonidine is 0.45 mg/day and for debrisoquine it is 20 mg/day. In mild to moderate hypertension only prazosin (up to 6 mg/day) or hydralazine (up to 100 mg/day) are also suitable alternatives to beta blockade.

Step 3 The prior introduction of a diuretic and a beta blocker allows the commencement of a peripheral vasodilator at Steps 3 and 4 without the development of cardiac stimulation or refractoriness due to secondary fluid retention or hyperreninemia. The synergistic actions of propranolol and hydralazine have been well documented. Although the properties of beta blockers are not as strongly complementary to those of prazosin as they are to those of hydralazine their hypotensive effects summate with that of prazosin and the following synergistic interactions occur[4]: (1) the tendency for prazosin induced orthostatic tachycardia is countered by the negative chronotropic action of beta blockers (2) the blood pressure in the standing position tends to be higher than in the supine position with beta blockers but lower with prazosin (3) prazosin will prevent the predominance of unopposed alpha-constrictor vascular tone consequent upon blockade of the beta 2 receptor mediated vasodilator mechanism (4) beta blockers may prevent the provocation of angina pectoris by prazosin.

In the presence of adequate beta blockade the dose of prazosin may be increased to 30 mg/day and that of hydralazine to 200 mg/day (or higher in rapid acetylators with normal renal function). However such doses may not be well tolerated in patients who because of contraindications to beta blocker therapy were given one of the other sympatholytic agents at Step 2. Except in regard to the negative chronotropic effect of clonidine additive but not synergistic relationships exist between these agents and prazosin or hydrala-

64 Ram C V S Holland O B Fairchild C and Gomez Sanchez C E Withdrawal syndrome following cessation of guanabenz therapy J Clin Pharmacol 19 148 1979

65 MacCarthy E P and Stokes G S Overshoot hypertension following withdrawal of guanfacine a clonidine congener (Personal communication)

66 Whitsett T L Chrysant S G Dillard B L and Anton A H Abrupt cessation of clonidine administration a prospective study Am J Cardiol 41 128› 19 8

67 Oates H F Stoker L M Monaghan J C and Stokes G S Withdrawal of clonidine effects of varying dosage or duration of treatment on subsequent blood pressure and heart rate responses J Pharmacol Exp Ther 206 268 1978

68 Oates H F Stoker L M and Stokes G S Studies in the rat on the haemodynamic overshoot response to withdrawal of guanfacine or clonidine treatment Clin Exp Pharmacol Physiol 6 61 1979

69 Salzmann R The effects of treatment and of withdrawal of treatment with guanfacine and clonidine on blood pressure and heart rate in normotensive and renal hyper ten ive rats J Pharm Pharmacol 31 212 1979

70 Graham R M Gain J M W and Stokes G S The use of clonidine by intramuscular injection in the treatment of hypertension Aust N Z J Med 7 131 1977

71 McMahon F G Ryan J R Jain A K Vargas R and Vanous S K Guanabenz in essential hypertension Clin Pharmacol Ther 21 272 1977

72 Mitchell J R Cavanaugh J H Arias L and Oates J A Guanethidine and related agents III Antagonism by drugs which inhibit the norepinephrine pump in man J Clin Invest 49 1596 1970

73 Stokes G S Graham R M Cain J M, and Davis P R Influence of dosage and dietary sodium on the first-dose effects of prazosin Br Med J 1 1507 1977

74 Stokes C Monaghan J Frost G and MacCarthy P Analysing responsiveness to prazo in in renal failure new pharma odynamic approa h Proceedings of the 6th Scientific Meeting of the International Society of Hypertension Got borg June 19 3 Abstract 313

75 Moulds R F W and Jauernig R A Mechan m of prazosin collapse Lancet 1 200 1977

76 Dargie H J Dollery C T and Daniel J Labe a in resistant hypertension Br J Clin Pharmacol Suppl 3 7›1 1976

77 Stokes G S Frost G W Graham R M and MacCarthy E P Indoramin and prazosin as adjuncts to beta adrenoreceptor blockade in trea ing hypertens Clin Pharmacol Ther 25 783 1979

78 Beilin L J and Juel-Jensen B E Alpha and beta adrenergic blockade in hypertension Lancet 1 9 1972

79 Frishman W, Silverman, R Strom J Elkayam U and Sonnenblick E Clinical pharmacology of the new beta adrenergic blocking drugs 4 Adverse effects—ch ing a beta adrenoreceptor blocker Am Heart J 98 1979

80 Waal Manning H J Can beta blockers be used in diabetic patients? Drugs 17 157 1979

81 Nyberg G Graham R M and Stokes G S The effect of mental arithmetic in normotensive and hypertensive subjects and its modification by beta adrenergic receptor blockade Br J Clin Pharmacol 4 4›6 1977

82 Greenblatt D J and Koch Weser J Adverse reactions to propranolol in hospitalized medical patients A report from the Boston Collaborative Drug Surveillance Program Am Heart J 86 4 8 19 3

83 Heel R C Brogden R N Speight T M and Avery G S Atenolol A review of its pharmacological properties and therapeutic efficacy in angina pectoris and hypertension Drugs 17 4›5 1979

84 Zacest R Gilmore E and Koch Weser J Treatment of essential hypertension with combined vasodilation and beta adrenergic blockade N Engl J Med 286 1972

85 Gutkin M Das, B Chin B K Mersey K and Mc linger R S Synergistic effects of hydralazine and alpha or beta adrenergic blockers the role of plasma renin activity J Clin Pharmacol 17 509 1977

20 Dunstan H P., Tarazi R C., and Bravo E L False tolerance to antihypertensive drugs *in* Systemic Effects of Antihypertensive Agents, M P Sambhi, ed., New York 1976 Stratton Intercontinental, p 51

21 Oates H F., Stoker L M., Monahan J C., and Stokes G S The beta-adrenoceptor controlling renin release Arch Intern Pharmacodyn Ther 234 205 1978

22 Stokes G S., Weber M A and Thornell I R Beta blockers and plasma renin activity in hypertension B Med J 1 60 1974

23 Steele T H Mechanism of the uricosuric activity of ticrynafen, Nephron 23 (Suppl 1) 33 1979

24 Lau K., Stote R M., Goldberg M., and Agus Z S Mechanisms of the uricosuric effect of the diuretic tienilic acid (Ticrynafen) in man, Clin Sci Mol Med 53 379 1977

25 Prasad, D R., Weiner I M., and Steele T H Diuretic induced uricosuria interaction with pyrazinoate transport in man, J Pharmacol Exp Ther 200 58 1977

26 Gillies A H and Morgan, T O A double blind comparison of the effects of hydrochlorothiazide and tienilic acid (a diuretic with uricosuric properties) in hypertension Br J Clin Pharmacol 6 357 1978

27 Kelley W N Current therapy of gout and hyperuricemia Hosp Pract May 1976 p 69

28 Walker B., Capuzzi, D M., and Alexander F Hyperkalemia after triamterene in diabetic patient Clin Pharmacol Ther 13 643 1972

29 Kassirer J P., and Harrington, J T Diuretics and potassium metabolism a reassessment of the need effectiveness and safety of potassium therapy Kidney Int 11 505 1977

30 Goldner M G., Zarowitz H., and Akgun S Hyperglycaemia and glycosuria due to thiazide derivatives administered in diabetes mellitus N Engl J Med 262 403 1960

31 Mustala, O and Toivonen S Glucose tolerance and diuretics Lancet 1 901 1967

32 Lavender S and McGill, R J Non ketotic hyperosmolar coma and frusemide therapy Diabetes 23 247 1974

33 Dargie H J and Dollery C T Adverse reactions to diuretic drugs, *in* Meyler's Side-Effects of Drugs Vol VIII M Dukes ed Amsterdam Oxford 1975 Excepta Medica p 483

34 Suki, W N Effects of diuretics on calcium metabolism Mineral Electrolyte Metab 2 125 1979

35 Vlasses P H., and Ferguson, R K. Temporary ageusia related to captopril, Lancet 2 526 1979

36 Farrow P R., and Wilkinson, R. Reversible renal failure during treatment with captopril, Br Med J 1 1680 1979

37 Dunn F G., de Carvalho J G R., Kem D C Higgins J R and Frohlich, E D Pheochromocytoma crisis induced by saralasin relation of angiotensin analogue to catecholamine release N Engl J Med 295 605 1976

38 Kem H J Drayer J I Case D B Lopez Overjero J Wallace J M., Weber M A., and Laragh, J H A role for renin in rebound hypertension and encephalopathy after infusion of saralasin acetate (Sar¹ Ala Angiotensin II) N Engl J Med. 295 1175 1976

39 Castellion, A W., and Fulton, R W Preclinical pharmacology of saralasin Kidney Int 15 S11 1979

40 Alarcon-Segovia, D Walum K G Worthington, J W and Emmerson, W L. Clinical and experimental studies on the hydralazine syndrome and its relationship to systemic lupus erythematosus Medicine 46 1 1967

41 Limas, C J., and Freis E D Minoxidil in severe hypertension with renal failure effect of its addition to conventional antihypertensive drugs Am J Cardiol. 31 355 1973

42 Laroche le P., Hamet P., Beroniade V., and Kuchel O Minoxidil in severe hypertension Eur J Clin Pharmacol. 14 1 1978

43 Brooks C S and Bauer J H. Treatment of refractory hypertension with minoxidil, Cardiovasc Med. 4 633 1979

44 Marquez-Julio A., and Uldall, P R. Pericardial effusions associated with minoxidil Lancet 2 816 1977

45 Earhart R N Ball, J., Nuss, D D., and Aeling J L. Minoxidil induced hypertrichosis treatment with calcium thioglycolate depilatory South. Med. J 70 442 1977

46 Stokes G S Weber M A., Gain, J., Scott, A. I., Robert B A and Sheil, A. G R. Diazoxide-induced renin release in diagnosis of remediable renovascular hypertension Aust N Z J Med. 6 26 1976

47 MacCarthy E P., and Stokes G S Renal vein renin and saralasin testing in renovascular hypertension, Am Heart J 96 579 1978

48 Tarazi, R. C Vasodilators in hypertension spectrum of actions and counteraction. Cardiovasc Med. 3 1125 1978

49 Pohl, J E. F., and Thurston, H Use of diazoxide in hypertension with renal failure Br Med. J 4 142 1971

50 Nears D Thurston, H., and Pohl, J E F Development of extra pyramidal symptoms in hypertensive patients treated with diazoxide Br Med J 3 474 1974

51 Lewis G R. J., Morley K. D., Maslowski, A. H., and Bones P J Verapamil in the management of hypertensive patients, Aust. N Z J Med. 9 62, 1979

52 Vohra J K Clinical use of verapamil, Curr Therap 18 61 1977

53 Pederson O L., and Mikkelsen, E. Acute and chronic effects of nifedipine in arterial hypertension, Eur J Clin. Pharmacol. 14 375 1978

54 Raschack, M. Differences in the cardiac actions of the calcium antagonist verapamil and nifedipine Arzneim. Forsch. 26 1330 1976

55 Palmer R. F., and Lasseter K. C Sodium nitroprusside N Engl J Med. 292 294 1975

56 Jackson, R. V., Love J B., Parkin, W G., Wahlquist M. L., and Williams N S Use of a microprocessor in the control of malignant hypertension with sodium nitroprusside, Aust N Z J Med. 7 414 1977

57 Briant R. H., Reid, J L., and Dollery C T Interaction between clonidine and desipramine in man Br Med J 1 522 1973

58 Van Zwieten, P A. Reduction of the hypotensive effect of clonidine and alpha methyldopa by various psychotropic drugs Clin. Sci. Mol. Med. 51 411 1976

59 Hansson, L., Hunyor S N., Julius S., and Hoobler S W Blood pressure crisis following withdrawal of clonidine (Catapres, Catapresan) with special reference to arterial and urinary catecholamine levels and suggestions for acute management Am Heart J 85 605 1973

60 Hunyor S N., Hansson, L., Harrison, T S., and Hoobler S W Effects of clonidine withdrawal possible mechanisms and suggestions for management Br Med. J 2 209 1973

61 Reid J L., Dargie H. J., Davies D S., Wing L. M. H., Hamilton, C A., and Dollery C T Clonidine withdrawal in hypertension Lancet 1 1171 1977

62 Goldberg A. D Wilkinson P R., and Raftery E. B The overshoot phenomenon on withdrawal of clonidine therapy Postgrad. Med. J 52 128 1976

63 Burden, A. C., and Alexander C P T. Rebound hypertension after acute methyldopa withdrawal, Br Med. J 1 1056 1976

T Sustained reduction of cardiac impedance and preload in congestive heart failure with the antihypertensive vasodilator prazosin N Engl J Med **297** 303 1977

6 Braunwald E Vasodilator therapy—A physiologic approach to the treatment of heart failure N Engl J Med **297** 331 1977

7 Franciosa J A Pierpont G and Cohn J N Hemodynamic improvement after oral hydralazine in left ventricular failure Ann Intern Med **86** 388 1977

8 Aronow W S Lurie M Turbow M Whittaker K VanCamp S and Hughes D Effect of prazosin vs placebo on chronic left ventricular heart failure Circulation **59** 344 1979

9 Cohn J N and Franciosa J A Vasodilator therapy of cardiac failure I N Engl J Med **297** 27 1977

10 Cohn J N and Franciosa J A Vasodilator therapy of cardiac failure II N Engl J Med **297** 254 1977

11 Mason D T Afterload reduction and cardiac performance Physiologic basis of systemic vasodilators as a new approach in treatment of congestive heart failure Am J Med **65** 106 1978

12 Fries F D New treatment for congestive heart failure AM HEART J **97** 127 1979

13 Lakier J B, Khaja S and Stein P Rationale and use of vasodilators in the management of congestive heart failure AM HEART J **97** 519 1979

14 Arnold S B Williams R L Ports T A Baughman R A Benet L Z Parmley W W and Chatterjee K Attenuation of prazosin effect on cardiac output in chronic heart failure Ann Intern Med **91** 345 1979

15 Packer M, Miller J Corlin P and herman M V Hemodynamic and clinical tachyphylaxis to prazosin mediated afterload reduction in severe chronic congestive heart failure Circulation **59** 531 1979

16 Elkayam U Lejemtel T Mathur M Ribner H Frishman W Strom J and Sonnenblick E H Marked early attenuation of hemodynamic effects of oral prazosin therapy in chronic congestive heart failure (Abstract) Am J Cardiol **43** 403 1979

17 Arnold S Ports T Chatterjee K Williams R, Rubin S and Parmley W Rapid attenuation of prazosin mediated increase in cardiac output in patients with chronic heart failure (Abstract) Circulation **58** (suppl II) 11 1978

18 Walsh W and Greenberg B Late results of oral hydralazine in patients with refractory heart failure (Abstract) Circulation **60** 209 1979

19 Champy C and Gley E Sur la toxicite des extraits de corps juane Immunization rapide consecutive a l injection de patites doses de ces extraits (tachyphylaxie) Compt. Rencl Soc Biol. **71** 159 1911

20 Waud D R Pharmacological receptors Pharm Rev **29** 59 1968

21 Goldstein A Aronow L and Kalman S M Principles of Drug Action New York 1968 Harper & Row p 558

22 Watkins L Jr Burton J A Haber E Smith F W and Barger A C The renin angiotensin aldosterone system in congestive heart failure in conscious dogs J Clin Invest **57** 1606 1976

Primary myocardial disease, diabetes mellitus and small vessel disease

In a recent comprehensive study on primary myocardial disease Shirey and associates included among their group of 133 patients with primary myocardial disease 12 patients with diabetes mellitus Based on biopsy findings—autopsies were performed in two diabetic patients only—the authors question the possible role of small vessel disease in the pathogenesis of diabetic heart disease An opposite view was taken by others and by us Fearce and colleagues obtained myocardial specimens by ventricular septal biopsy in eight patients with maturity onset diabetes Coronary angiography performed in four patients was normal in two patients with angina probably normal in one patient with congestive heart failure and with diffuse disease in one patient with cardiomegaly Focal myocardial fibrosis and varying degree of intimal proliferation of small vessels (30 to 100 microns) were present in all patients The negative results reported by Shirey and associates may be due to technical difficulties or to the imperfection of the technique Even the authors felt that it seems difficult to derive from biopsies the prevalence and significance of small vessel disease Biopsy technique missed focal changes of the myocardium in 33 of 133 patients (25%) The sample obtained by needle biopsy may or may not be representative of the whole Therefore autopsy remains the best method in evaluating the changes taking place in the myocardium We obtained parafin blocks of 87 hearts from 50 diabetic nonhypertensive patients, and from 37 nondiabetic patients Four blocks were taken from seven areas Each block was sectioned at 6 microns and four sections were stained with hematoxylin-eosin and Verhoeff Van-Gieson stain Small coronary artery involvement (20 to 150 microns) found in 36 diabetic patients (72%) consisted of (1) endothelial proliferation (2) subendothelial fibrosis (3) exudative deposits of hyaline in the intima and (4) atheromatous thickening with cholesterol clefts and hyalinized intima Intramural vessel involvement alone was found in 18 patients (36%) The heart was enlarged—over 400 g males, and over 35 females in eight patients with small artery involvement and normal extramural coronary arteries In the control group of 32 nondiabetic patients involvement of the intramural arteries only was detected in four cases Since the control group presented a variety of clinical manifestations there is the possibility that intramural vessel involvement was the consequence of underlying clinical disease The small artery changes are not specific for diabetes mellitus, but they

0002 8703/80/110754 + 03$00.20/0 © 1980 The C V Mosby Co

When is loss of responsiveness to a vasodilator agent in the patient with congestive heart failure due to tachyphylaxis?

One of the subjects of important debate at the recent meetings in Anaheim involved vasodilator therapy for advanced congestive heart failure Almost 30 years ago dibenamine was shown to decrease right atrial and pulmonary pressure in patients with congestive heart failure and patients with acute pulmonary congestion and edema refractory to conventional therapy were then reported to respond dramatically to the administration of adrenergic or ganglionic blocking agents Burch and colleagues pointed out that the salutary response in this situation was much more likely to reflect venous dilatation than afterload reduction There is continued broad agreement that a beneficial response occurs with the acute administration of a number of additional agents. With attempts at chronic therapy debate now centers on how well sustained responses to individual agents are a recurrent theme appears to be that agents lose their effectiveness with time Unfortunately the term tachyphylaxis has been employed by some to describe this loss of responsiveness in patients with heart failure providing a contemporary example of how the misuse of word can confuse issues

When should we employ the term tachyphylaxis rather than the more humble terms refractory resistant or unresponsive? What additional information does this complicated word carry if any? If it is merely a synonym for refractory or unresponsive we clearly should not use it

As used in pharmacology tachyphylaxis connotes an element of specificity which unresponsiveness does not Vascular smooth muscle for example may fail to dilate in response to an agent because the reduced blood flow is not due to active vasoconstriction but rather to some mechanical problem such as edema of the vessel wall an alteration in excitation-contraction coupling or the contractile apparatus itself so that vasodilatation is not possible In these cases the refractory state would be generalized and no agent would induce a response Alternatively response to a specific agent might be lost because of a change in the number or affinity of the available receptors for that agent or because a change in the physiology of the milieu makes the agent ineffective An excellent example of the latter phenomenon was provided by the studies of Watkins and associates. When acute CHF was induced in the dog converting enzyme inhibition reduced blood pressure strikingly Over the next several days arterial blood pressure and by inference afterload no longer responded to the inhibition Plasma renin activity rose sharply following the acute onset of CHF and gradually returned to control value as sodium retention occurred accounting for the resistance of blood pressure to the inhibitor A similar sequence could well account for the loss of effectiveness of alpha adrenergic blocking agents. In this case the loss of responsiveness would be specific for a single agent and the system would be capable of responding to other agents. The term tachyphylaxis should be applied to this specific case in which responsiveness is lost to only one agent thus discriminating the loss of response from a generalized refractory state

This distinction clearly would have important implications for pathophysiology and therapy Until alternative agents have been assessed and have been shown to be ineffective the term tachyphylaxis should not be applied. One cannot help but wonder how much of the debate would be resolved if we knew whether patients who apparently become resistant to prazosin or hydralazine have indeed become resistant to all agents Does resistance to one agent preclude effective use of another? Anecdotal, clinical experience indicates that this is not so but none of the formal studies have attempted to answer this important question

The notion of course applies to other therapeutic maneuvers Investigators and clinicians involved in the treatment of problems as diverse as cardiac arrythmia hypertension recurrent urinary tract infections, and leukemias often face the problem of the patient whose condition has become refractory to a specific agent—fortunately most have resisted the temptation to replace the general term with tachyphylaxis

Leonard G Meggs M.D
Normam K Hollenberg M.D Ph.D
Harvard Medical School and
Peter Bent Brigham Hospital
Boston Mass

REFERENCES

1 Halmagyi, D., Felkai, B Ivanyi, J and Hetenyi, G Jr The role of the nervous system in the maintenance of venous hypertension in heart failure Br Heart J 14 101 1952.
2. Wheatley D Relief of acute left ventricular failure by Priscol," Br Med J 1 1174 1952.
3. Ellestad M. H., and Olson W H Use of intravenously given ganglionic blocking agents for acute pulmonary edema J.A.M.A 161 49 1956
4 Burch, G E., Leon Galindo J., and Cronvich J A New treatment for chronic intractable congestive heart failure AM HEART J 91 735 1976
5 Miller R R., Awan A.A., Maxwell K S., and Mason D

0002-8703/80/110753 + 02$00 20/0 © 1980 The C V Mosby Co

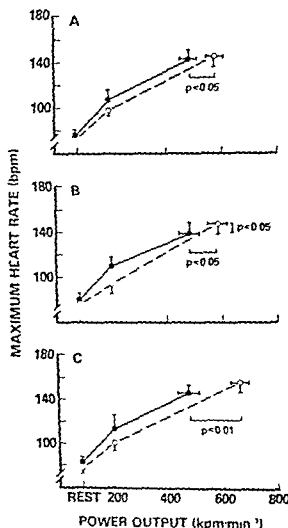


Fig 1 Mean (± SEM) maximal heart rate and power output changes over (A) 0 to 7 months (n = 17) (B) 0 to 12 months (n = 1) and (C) 0 to 21 months (n = 7)

for at least 7 months. 10 patients continued in the program for 12 months, and continued for 21 months. Their mean age (x ± 1 SD) was 2 6 ± 8 4 years 13 had suffered a myocardial infarction three of whom subsequently had bypass surgery. Two patients had undergone bypass surgery without a prior infarction and two had angina pectoris without infarction or bypass. Exercise testing was carried out on a calibrated electrically stabilized load-cycle ergometer on entry and 7 12, and 21 months later changes in heart rate systolic blood pressure rate pressure product expired ventilation and power output were analyzed over 0 to 7 0 to 12, and 0 to 21 months. The exercise program consisted of 30 to 40 minutes of treadmill walking and cycle ergometry and 20 to 30 minutes of volleyball. The patients met twice weekly and were expected to exercise at home on at least two other days. The intensity of exercise was prescribed by the method of Balke supervision was provided by two exercise leaders and a physician

Following regular participation in the program for as long as 21 months, there were no changes in weigh resting heart rate but significant ($p < 0.05$) increases were observed in resting systolic blood pressure and rate pressure product by 12 and 21 months. No significant changes were observed in the cardiorespiratory responses at a constant submaximal power output (200 kpm min.⁻¹) at any time, although heart rate at 200 kpm min⁻¹ was lower at each test (0 to 7 months = 9 bpm, 0 to 12 months = −15 bpm 0 to 21 months = −12 bpm. Significantly higher maximum power outputs (x ± 1 SE) were observed (Fig 1) at the end of 7 months participation (489 ± 31 to 579 ± 33 kpm min.⁻¹) over 12 months (ff to 575 ± 39 kpm min) and over 21 months ((to 6?1 ± 28 kpm min) Maximum heart rate (x ± 1 SE) increased over each period but significantly only over the 0 to 12 months period (138 ± 9 to 14 ± 8 bpm) there were no significant changes in maximal systolic blood pressure rate-pressure product or expired ventilation at any time

The proportions of females and males referred to the exercise rehabilitation program were similar to those reported for other programs in North America and presumably reflect the lower incidence of coronary heart disease in females and perhaps a smaller number of exercising North American middle aged females than males. The dropout rate was somewhat higher than that observed in male cardiac patients exercising at the same institution. The increase in maximal power output and maximal heart rate was similar to that observed in male cardiac patients. The submaximal responses during progressive exercise testing, although not statistically significant, were similar to those reported in the literature for male cardiac patients the decrease in similar to that observed in 190 male cardiac patients at the institution who within 6 months, demonstrated a significant (p < 0.05) decrease of 12% in submaximal heart rate with a similar exercise prescription (N Oldridge unpublished data). All 17 patients claimed that they were able to carry activities of daily living with greater self assurance and fewer problems than before entering the program. This qualitative subjective improvement in their daily life should be considered at least as important an effect of training as a quantitative improvement found during submaximal work or in maximal power output. These observations suggest that physical conditioning plays as important a role in the rehabilitation of selected female coronary heart disease patients as it does in male patients, particularly in their ability to carry out activities of daily living with a renewed sense of confidence

N B Oldridge PhD
D LaSalle MSc
N L Jones, MD
Departments of Physical Education and Medicine
McMaster University
Hamilton, Ontario
Canada

REFERENCES

1. Clausen J P Circulatory adjustments to dynamic exercise and effect of physical training in normal subjects and in patients with coronary artery disease, Prog Cardiovasc Dis. 18 459 1976
2. Jones, N L, Campbell, E J M Edwards, R H T and Robertson, D G Clinical exercise testing Philadelphia 1975 W B Saunders p 52
3. Balke B Prescribing physical activity in Ryan A J and Allman F L, Eds. Sports Medicine New York 1974 Academic Press, p 505
4. Bruce E H., Frederick R Bruce R. A., and Fisher L

frequency and severity in this disease make them a highly characteristic feature The small stiff heart causing onset of acute pulmonary edema was reported in diabetic patients when both intramural and extramural coronary arteries were severely involved Functional derangements in the microcirculation of diabetic patients as a result of small vessel involvement might represent one of the basic causes of myocardial impairment and conduction disturbances.

The changes taking place in the myocardial circulation and metabolic abnormalities, including deposits of PAS material in the left ventricular interstitium might determine progression of the process A basic departure from the concept—that the myocardial microcirculation in diabetics is different from all the other organs—is taking place Recently there have been reports describing thickening and proliferation of the capillary basement membrane as a generalized phenomena taking place in many organs including the heart For the first time *diabetic capillary microaneurysms have been observed* in the hearts of three of six diabetic patients

A protracted period of controversy seems to be approaching its end The intramural circulation may ultimately be recognized as an important factor in the pathogenesis of diabetic heart disease

Samuel Zoneraich MD FACC
Gertrude Silverman MD
Olga Zoneraich MD FACC
State University of New York at Stony Brook
Clinical Campus
Queens Hospital Center
Long Island Jewish Hillside Medical Center
Jamaica N Y 1143

REFERENCES

1 Shirey E K Proudfit W L and Hawk W A Primary myocardial disease Correlation with clinical finding angiography and biopsy diagnosis Follow up of 139 patients AM HEART J 99 198 1980
2 Blumenthal H T Alex M and Goldenberg S A study of lesions of the intramural coronary artery branches in diabetes mellitus Arch Pathol 70 27 1960
3 James T N Small arteries of the heart The George Brown Memorial Lecture Circulation 56 ? 19/7
4 Halkin H and Ravid M Involvement of the intramural coronary circulation in diabetic angiopathy Isr J Med Sci 8 773 1976
5 James T N Pathology of small coronary arteries Am J Cardiol 20 6 9 19 6
6 Ficarce M B Bullock R T and Kizziar J C Myocardial small vessel disease in patients with diabetes mellitus Circulation 48(Suppl 4) 6 1973
7 *Hamby R I Zoneraich S and Sherman L Diabetic* cardiomyopathy JAMA 229 1749 19/4
8 Zoneraich S Silverman G and Zoneraich O Small coronary artery disease in diabetes mellitus Circulation 55(Suppl III) 1?4 19/7
9 Zoneraich S and Silverman G Myocardial small vessel dis in diabetic patients *in* Diabetes and the Heart S Zoneraich ed Springfield Ill 1978 Charles C Thomas pp 3-18
10 Zoneraich S Angina pectoris in diabetic patients with normal coronary arteries JAMA 241 231 19 9
11 Zoneraich S Silverman G and Zoneraich O Small stiff heart in diabetes mellitus (Abstract) Am J Cardiol 41 613 19/8
12 Badeer H S Zoneraich A Pathogenesis of cardiomyopathy in diabetes mellitus *in* Diabetes and the Heart S Zoneraich ed Springfield Ill 19/8 Charles C Thomas pp 26-45
13 Zoneraich S Zoneraich O and Rhee J J Left ventricular performance in diabetic patients without clinical heart disease Evaluation by systolic time intervals and echocardiography Chest 72 748 19/7
14 Zoneraich O and Zoneraich S A vectorcardiographic study of spatial P QRS and T loops in diabetic patients without clinical heart disease J Electrocardiology 10 20/ 19/7
15 Zoneraich S Zoneraich O Rhee J J Liao C Patel M M Electrocardiogram in diabetic patients with no apparent cardiac involvement Echocardiographic correlations Third International Congress on Electrocardiology Brussels 19/6 pp 118-119
16 Regan T J Haider B and Lyons M M Altered ventricular function and metabolism in diabetes mellitus *in* Zoneraich S ed Diabetes and the Heart Springfield Ill 1978 Charles C Thomas, Publisher pp 1?3 136
17 Silver M D Huckell V F, and Lorber M Basement membranes of small cardiac vessels in patients with diabetes and myxedema preliminary observations Pathology 9 213 1977
18 Fischer V W Barner H B and Leskin M L Capillary basal laminar thickness in diabetic human myocardium Diabetes 28 713 19/9
19 Factor S M Okun E M and Minase T Capillary microaneurysms in the human diabetic heart N Engl J Med 7 384 1980

Exercise rehabilitation of female patients with coronary heart disease

Cardiorespiratory responses to physical conditioning have been extensively studied in male coronary heart disease patients but little information is available for female cardiac patients undergoing similar programs Twenty eight female cardiac patients were referred to a supervised exercise rehabilitation program between March 1973 and March 1977 (approximately 8% of male patient referrals over the same time period) 17 of these patients participated in the program

0002 8 03/80/110 5? + 03?00 30 0 © 1980 The C V Mosby Co

hyperplasia presumably resulting from vasoconstriction has been the basis for vasodilator therapy for primary pulmonary hypertension Early reports demonstrated pulmonary vasodilatation in pulmonary hypertensive patients who received intravenous infusions of isoproterenol or tolazoline but systemic side effects are common and the clinical usefulness of this therapeutic approach is limited Only a handful of patients have been reported to obtain benefit from sublingual isoproterenol [1] and the duration of action after each dose is short Furthermore the absence of any long term follow up of patients treated in this manner speaks of its not being of lasting help over the long haul Nevertheless the demonstration that the hypertensive pulmonary arterial bed can dilate in response to the administration of vasodilators was encouraging and it initiated a search for more effective and better tolerated pulmonary vasodilators

Diazoxide a potent systemic antihypertensive agent has recently been demonstrated to be a pulmonary vasodilator in four patients with primary pulmonary hypertension In two separate reports diazoxide given intravenously caused a reduction in pulmonary arteriolar resistance and an increased cardiac output without affecting systemic blood pressure Surprisingly the drug was also effective when administered orally and hemodynamic and symptomatic improvement persisted in the patients who were maintained on chronic oral therapy This drug however is not given without hazard a death was recently reported after intrapulmonary diazoxide was given to a patient with primary pulmonary hypertension

In a recent case report a pati[illegible]nt with primary pulmonary hypertension evidenc[illegible] h[illegible]m[illegible]dynamic improvement with the intravenous injecti[illegible]n [illegible] phentolamine an α adrenergic inhibitor This patient [illegible] eated with oral phentolamine and on repeat catheter[illegible] seven months later a persistent response wa[illegible] d[illegible] [illegible]rente[illegible]

We recently re[illegible]p[illegible]rted our experience using oral hydralazine in four patients with primary pulmonary hypertension In those patients the administration of hydralazine 50 mg by mouth every six hours for 48 hours resulted in a reduction in pulmonary arteriolar resistance and an increase in cardiac ou[illegible]put at rest Similar changes were also observed in three patients who were also studied during a period of exercise on a bicycle ergometer Repeat cardiac catheterizations were performed four to six months after beginning chronic oral hydralazine therapy and the hemodynamic improvement persisted Our patients also had symptomatic improvement and this dose of hydralazine was tolerated without significant side effects Since the publication of our original experience we have had the opportunity to study three additional patients with this disease two of these had responses comparable to those in our original series

Despite the inherent risks it is our current practice to perform right heart catheterization before and after instituting hydralazine therapy on all patients who are referred to us with the diagnosis of primary pulmonary hypertension We have tested our patients for pulmonary vascular responsiveness to the administration of 100% oxygen (seven patients) and intravenous phentolamine (four patients) but we have not found either modality useful

The temptation to empirically treat pulmonary hypertensive patients with vasodilators must be strongly resisted Hemodynamic changes may be the only evidence of improvement It is clear that not all patients will respond to this therapeutic approach and no drug should be given to a patient without the demonstration of both its indication and its efficacy Systemic hypotension could prove fatal to these often hemodynamically fragile patients Furthermore vasodilator therapy could augment the right-to-left intracardiac shunting in patients with pulmonary hypertension resulting from an unsuspected patent foramen ovale and these drugs should be used cautiously in this setting.

The demonstration that oral vasodilator therapy can lead to hemodynamic improvement in some patients with primary pulmonary hypertension has raised several important questions

1 Which vasodilator is the safest and most effective for pulmonary hypertension?

2 What is the optimal dose of a vasodilator for patients with primary pulmonary hypertension? It is now well known that there is a marked variability in the dose requirements of vasodilators for left ventricular failure and undoubtedly a comparable situation exists in pulmonary hypertension

3 What is the role of concomitant anticoagulant therapy for primary pulmonary hypertension? Although anticoagulation does not appear to cause hemodynamic or symptomatic improvement the increased risk of thromboembolic disease in this setting may be a justification for anticoagulant therapy Our practice however is currently to withhold anticoagulation unless a clear indication is present.

4 Can the response to vasodilator therapy yield insight into the pathogenesis of this disease? Clarification of the mechanisms of pulmonary vasodilation could not only lead to the discovery of more effective pulmonary vasodilators but it could also provide information concerning the mechanisms of vasoconstriction in the abnormal pulmonary vascular bed

The answers to these questions will undoubtedly lead to newer approaches to the treatment of this tragic disease

Lewis J Rubin, MD
Robert H Peter MD
Department of Medicine
Duke University Medical Center
Durham N C [illegible]

REFERENCES

1 Dresdale D T Schultz M and Michtom R J Primary pulmonary hypertension I Clinical and hemodynamic study Am. J Med. 11 686 1951
2. Daoud F S Reeves J T., and Kelly D B Isoproterenol as a potential pulmonary vasodilator in primary pulmonary hypertension Am J Cardiol 42 817 19[illegible]
3 Inglesby T V., Singer J W and Gordon, D Abnormal fibrinolysis in familial pulmonary hypertension Am J Med 55 5 1973
4 Walcott G Burchell, H B and Brown A L. Primary pulmonary hypertension Am J Med. 49 70 1970
5 Lebrec D Capron J P., Dhumeaux D and Benhamou J P Pulmonary hypertension complicating portal hypertension Am Rev Resp Dis. 120 849 1979
6 Shettigar V R Hultgren H N Specter M Martin R and Davies D H Primary pulmonary hypertension favorable effect of isoproterenol. N Engl. J Med 295 1414 1976
7 Wang S W S Pohl, J E F Rowlands, D J and Wade E. G Diazoxide in the treatment of primary pulmonary hypertension Br Heart J 40 5[illegible] 1978

D Comparison of active participants and dropouts in CAPRI cardiopulmonary rehabilitation programs Am J Cardiol 37 53 1976
5. Gordon T Kannel W B Hjortland M J and McNamara P M Menopause and coronary heart disease The Framingham study Ann Intern Med 89 157 1978
6 Oldridge N B Wicks J R Hanley C Sutton J R and Jones N L Non-compliance in an exercise rehabilitation program for men who have suffered a myocardial infarction Can Med Assoc J 118 361 1978
7 Sanne H Exercise tolerance and training of non selected patients after myocardial infarction Acta Med Scand Suppl 551 1973

Of the Q wave and myocardial infarction

There is an erroneous tendency to assume that only a Q wave abnormality is necessary to establish electrocardiographic diagnosis of myocardial infarction Thus some clinicians consider that unless a Q wave of infarction is present myocardial infarction does not exist Nothing could be further from the truth than that concept Those who subscribe to this concept and so frequently include it in their publications fail to realize that the time course of the Q wave occurs early in the depolarization process of the ventricles Therefore only infarction in the myocardial area depolarized early in the activation of the electric cycle can be expected to display abnormal Q waves in the ECG But the QRS complex continues on beyond the Q wave time in the time course of the entire depolarization process Therefore what about infarcts in the areas of the ventricle which are depolarized late and last durin the depolarization process? How could these infarcts change the early portions of the QRS complex or produce or change the Q wave? Obviously they don t Only the late or later parts of the QRS complex are abnormal when infarction occurs in myocardial areas depolarized late in the activation process This has been clearly shown and reported a number of years ago Therefore the lack of Q wave abnormalities does not exclude ECG evidence of myocardial infarction involving those parts of the ventricle depolarized late or last The absence of a Q wave abnormality only excludes evidence for infarction of areas of the ventricular myocardium depolarized early Furthermore it should be remembered that infarction of portions of the myocardium depolarized early may produce abnormalities of the early portions of the QRS complex other than the development of Q waves.

George E Burch M.D
Tulane University School of Medicine and Charity Hospital of Louisiana
New Orleans La

REFERENCES

1 Burch G E Horan L G Ziskind J and Cronvich, J A A correlative study of postmortem electrocardiographic and spatial vectorcardiographic data in myocardial infarction Circulation 18 325 1958
2 Burch, G E and Winsor T A primer of electrocardiography 6th edition Philadelphia 1972 Lea & Febiger

Primary pulmonary hypertension new approaches to therapy

Thirty years after its original clinical description primary pulmonary hypertension remains a disease of unknown cause and the few clues to its pathogenesis have not generally led to useful therapeutic modalities. The association of pulmonary hypertension with connective tissue diseases suggests an immunologic or inflammatory process but corticosteroids and cytotoxic drugs have no effect on the course of this disease Some investigators have postulated that microemboli possibly resulting from a hereditary defect in fibrinolysis cause the extreme elevations in pulmonary arterial pressures which are often seen in patients with this disease but anticoagulant therapy has not met with success. The exacerbation of pulmonary hypertension during pregnancy and the association of pulmonary hypertension with portal hypertension have led some observers to believe that the disease is the result of a hormonal abnormality To date however no specific defect has been demonstrated

The pathologic finding of pulmonary arteriolar muscle

0002-8703/80/110757 + 03$00.30/0 © 1980 The C V Mosby Co

washings. While hepatitis B has been transmitted to non human primates by subcutaneous or intravenous injection of HBs Ag positive saliva [illegible] intranasal and intra-oral installation did not result in infection. The possibility of HBs Ag in saliva reaching the blood of a mouth to mouth operator through small mucosal cracks is suggested by the report of transmission of hepatitis B by a human bite. Although the transmission of hepatitis B after mouth to-mouth contact of a person with a patient carrying HBs Ag in his blood or saliva has not been reported it would seem prudent to provide mouth to-mouth contacts of HBs Ag positive individuals with the same prophylaxis offered to those exposed to hepatitis B through inadvertent needle puncture from patients known to be HBs Ag positive. Such prophylaxis consists of [illegible] hepatitis B immune globulin given intramuscularly in a dose of 0.5 mL/kg body weight administered as soon as possible and repeated in [illegible] days.

Concern has also been expressed about the risk of transmitting hepatitis B via HBs Ag positive saliva that has contaminated the mannequins used to train individuals in CPR. Osterholm and colleagues studied 22 individuals who had participated in a CPR training programme. One of the students developed hepatitis B eight days later and carried HBs Ag in his blood and saliva but none of the contacts acquired hepatitis B. There was also no transmission of hepatitis to 23 individuals after mouth to-mouth contact with a CPR mannequin used by the instructor who subsequently developed hepatitis non A, non B. Another fortuitous experiment was the exposure of 12 students to HBs Ag positive saliva via contact with contaminated musical instruments. Although the instruments were not cleaned between use by the students and the HBs Ag [illegible] no transmission of hepatitis B [illegible] R training mannequins have not been [illegible] transmission of hepatitis B [illegible] mannequin's oral surface be clea[illegible] and that the manne[illegible] cleaned after each training [illegible]

[illegible] be transmitted from person to [illegible] the upper respiratory tract [illegible] pharyngeal secretions of persons [illegible] Although the paucity of reported [illegible] of meningococcal infection by mouth [illegible] that the risk of such transmission [illegible] mouth to-mouth contacts is heightened because [illegible] infection may be rapidly fatal. Jacobson and Fraser recommended that mouth to-mouth contacts of patients with meningococcal infection be given the same chemoprophylaxis with rifampicin, sulfadiazine or minocycline as other close contacts. However there may be a very brief period of colonization of the upper respiratory tract before the onset of meningococcal infection. To eradicate a potential [illegible] bacteremia in the mouth to-mouth contact Artenstein recommended procaine penicillin intramuscular [illegible] 500 000 units three times daily for two days, followed by orally administered penicillin V 500 mg three times daily for eight days. However Artenstein's regimen may be ineffective because meningococcal infection has been reported in close but not mouth to-mouth contacts receiving intramuscular procaine penicillin and benzathine penicillin for chemoprophylaxis. When faced with this dilemma I have recommended that the mouth to-mouth operator be admitted to hospital and started on 12 million units of penicillin intravenously in divided doses over [illegible] hours after [illegible] has been drawn for culture. The mouth to-mouth operator is discharged two days later if no symptoms develop and the cultures are sterile. Although this approach may seem overzealous, my experience has been that [illegible] the mouth to-mouth operator allays much of the [illegible] usually engendered by the exposure to a patient with meningococcal infection.

The seemingly very small risk of transmission of [illegible] from patient to operator during mouth to-mouth resuscitation is no reason to abandon mouth to-mouth resuscitation. However more frequent documentation of the [illegible] of such contacts with patients harboring various [illegible] would allow a better appreciation of the risk involved.

Michael R. Ach[illegible] MB FRCP(C)
Associate Professor
Department of [illegible]
McMaster University
[illegible]
Department of Medicine
St. Joseph's Hospital
Hamilton, Ontario, Canada
[illegible]

REFERENCES

1. Comroe JH [illegible] In comes the good air. Part II. Mouth to-mouth method. Am Rev Resp Dis 119 [illegible] 1979
2. Heilman, K. M., and Muschenheim, C. Primary cutaneous tuberculosis resulting from mouth to-mouth respiration. N Engl J Med 273 1035 1965
3. Feldman H A. Some recollections of the meningococcal disease. The first Harry F Dowling lecture. JAMA 220 1107 1972
4. Dienstag J L, Szmuness, W, Stevens C E, Purcell, R. H. Hepatitis A virus infection: new insights from sero-epidemiologic studies. J Infect Dis 137 [illegible] 1978
5. Krugman S., Giles, J P., and Hammond, J. Evidence for two distinctive clinical, epidemiological, and immunological types of infection. JAMA 200 365 1967
6. Villarejos, V M, Kirsten P H, Visona K A, Gutierrez, D., and Rodriguez, A. Role of saliva, urine and feces in transmission of type B hepatitis. N Engl J Med 291 1375 1974
7. Bancroft, W., Snitbhan R., Scott R M, Tingpalapong M., Watson W T., Tanticharoenyos, P, Karwacki J J, and Srimarut, S. Transmission of hepatitis B virus to gibbons by exposure to human saliva containing hepatitis B surface antigen. J Infect Dis 135 79 1977
8. Alter H J., Purcell R H., Gerin, J L., London, W, Kaplan, P M., McAuliffe V J, Warner J., and Holland P V. Transmission of hepatitis B to chimpanzees by hepatitis B surface antigen positive saliva and semen. Infect. Immun 16 928 1977
9. MacQuarrie M B., Forghani, B., and Wolochow D A. Hepatitis B transmitted by a human bite. JAMA 230 723 1974
10. Stiehm E. R. Standard and special human immune serum globulins as therapeutic agents. Pediatrics 63 [illegible] 1979
11. Davis, G E. Promiscuous Resus Annies—a public health problem? A plastic Typhoid Mary. J Maine Med Assoc 69 214 1978

Klinke W P., and Gilbert J A L Diazoxide in primary pulmonary hypertension N Engl J Med 302 91 1980
Rubino J M., and Schroeder J S Diazoxide in the treatment of primary pulmonary hypertension Br Heart J 42 362 1979
10 Ruskin J N and Hutter A M., Jr Primary pulmonary hypertension treated with oral phentolamine Ann. Intern Med. 90 772, 1979
11 Rubin L J and Peter R H Oral hydralazine therapy for primary pulmonary hypertension N Engl. J Med 302 69 1980

of viral nephritis

is still doubt in the minds of many physicians and even me nephrologists as to whether or not virus will infect dneys. Viral nephritis due to the Coxsackie B virus has been ed However it is well known that renal tissue ides a good culture medium for the picornaviruses The o virus is grown on kidney tissue culture and this is rtainly true for other viruses of this same group namely the kie viruses. This is proof enough that at least the infect renal cells.

George E Burch M D
Tulane University School of Medicine
and Charity Hospital of Louisiana
New Orleans La

Sun S C Burch G E., Sohal R S., and Chu K C Coxsackie B viral nephritis in mice and its autoimmune-like phenomena Proc Soc Exp Biol Med. 126 882, 1967
2. Burch, G E., Chu K C and Sohal, R. S Glomerulonephritis induced in mice by ECHO 9 virus, N Engl. J Med 279 1420 1968
3 Burch G E Chu K C Colcolough H L and Sohal, R. S Immunofluorescent localization of Coxsackievirus B antigen in the kidney observed at routine autopsy Am. J Med 47 36 1969
4 Burch G E., Tsui C Y., and Harb J M The early renal lesions of mice infected with encephalomyocarditis virus, Lab Invest 26 163 1972.
5 Burch, G.E., Harb J., and Hiramoto Y Coxsackie B viral infection of the human kidney J Urol. 112 714 1974

- hazards of mouth to mouth

ai

lthough it has been suggested that a fear of transmission of ection delayed the widespread acceptance of mouth to-outh breathing in the late 1940s scant attention is current given to the risks of transmitting infection from patient to rator during mouth to-mouth resuscitation The encour ement of prompt cardiopulmonary resuscitation (CPR) by th lay people and paramedical personnel in the community ll surely result in increasing numbers being exposed to oro-aryngeal secretions of patients who may be harboring an Cutaneous tuberculosis and meningococca infec n have been described in operators of mouth to mouth iscitation of patients with these diseases One can only ulate about the potential for transmission of other micro- during mouth to mouth resuscitation The risks of smitting hepatitis and meningococcal infection deserve special attention not only because of the potentially serious consequences of the infection but also because the management of such mouth to mouth contacts is debatable

Oropharyngeal secretions are not an important source for transmission of hepatitis A virus while hepatitis B is most likely to be transmitted by the parenteral route via blood blood products or blood drawing equipment However the mouth to-mouth route of transmission of hepatitis B is theoretically possible by two mechanisms

1 Hepatitis B has been transmitted to children by the oral administration of as little as 0 5 mL of hepatitis B surface antigen (HBs Ag) positive serum Thus bleeding about the oropharynx of the patient may result in blood containing HBs Ag being swallowed by the mouth to-mouth operator

2. HBs Ag may be found in both aliva and nasophar-

-8703/80/110759 + 03$00 30/0 © 1980 The C V Mosby Co

increased incidence of prematurity (22% one third of whom died) and stillbirth (13%) While liveborn morbidity was much less fetal or neonatal death was substantially greater with heparin use than with coumarin derivative exposure In addition maternal risk *may* be greater with heparin use (at least as previously administered)

Both of these agents carry substantial risks when used in pregnancy Because of this preconceptual counseling and if pregnancy occurs offering the option of therapeutic abortion appear to be the most prudent If anticoagulation and continuation of pregnancy are necessary the clinician is left to choose between unattractive alternatives Continued experience may demonstrate that heparin is in fact safer than our retrospective review would indicate For the present however coumarin derivatives remain a reasonable alternative if the *relative risks are explained carefully to the prospective parents*

Richard M Pauli M.D Ph D
Judith G Hall M D
Kathleen M Wilson B.A
Division of Medical Genetics
The Center for Inherited Diseases
Departments of Medicine and Pediatrics
University of Washington School of Medicine
The Children s Orthopedic Hospital and Medical Center
Seattle Wash

REFERENCES

1 Schofield F W Damaged sweet clover the cause of a new disease in cattle simulating hemorrhagic septicemia and blackleg J Am Vet Med Assoc 64 553 19[illegible]
2 von Sydow G Hypoprotrombinemi och hjarnskada hos barn till dikumarin behandlad moder Nord Med 34 1171 1947
3 Shaul W L, Emery H and Hall J G Chondrodysplasia punctata and maternal warfarin use during pregnancy Am J Dis Child 129 360 19[illegible]
4 Becker M H Genieser N B Finegold, M Miranda D and Spackman T Chondrodysplasia punctata Is maternal warfarin a factor? Am. J Dis. Child. 129 [illegible] 19[illegible]
5 Pettifor J M, and Benson R Congenital malformations associated with the administration of oral anticoagulants during pregnancy J Pediatr 86 459 19[illegible]
6 Pauli R M. Madden J D Kranzler K J Culpepper W, and Port R Warfarin therapy initiated during pregnancy and phenotypic chondrodysplasia punctata J Pediatr 88 506 19[illegible]6
7 Hall, J G Pauli R M and Wilson K M Maternal and fetal sequelae of anticoagulation during pregnancy—a review Am J Med 68 1[illegible] 1980

Osterholm M T., Bravo E R Crosson J T Hanson M Poleskey H F., Max B J., and Fifer E Z Lack of transmission of hepatitis B to humans after oral exposure to hepatitis B surface antigen positive saliva Morbid Mortal Weekly Rep 27 247 1978

Perras S T Poupard J A Byrne E B and Nast P R. Lack of transmission of hepatitis non A non B by CPR manikins N Engl J Med 302 118 1980

Osterholm M T., Max B J., Hanson M and Polesky H F Potential risk of salivary medicated viral hepatitis type B transmission from oral exposure to fomites J Hyg (Camb) 83 487 19 9

Khan A H Roland F P., and Carleton R A Cardio pulmonary resuscitation—potential danger of cross infection JAMA 241 ? 01 19 9

16 Conte J Decontamination of CPR training mannequins Morbid Mortal Weekly Rep 27 13_ 1978

17 Jacobson J A and Fraser D W A simplified approach to meningococcal disease prophylaxis, JAMA 236 1053 19 6

18 Edwards E A Devine L F Sengbusch, C H and Ward H W Immunological investigations in meningococcal disease III Brevity of Group C acquisition prior to disease occurrence Scand J Infect Dis 9 105 1977

19 Artenstein M S Prophylaxis for meningococcal disease JAMA 231 1035 1975

20 Anonymous Meningococcal meningitis Morbid Mortal Weekly Rep 17 178 1968

of anticoagulation during pregnancy

he recognition that coumarin derivative oral anticoagulants have adverse effects on the fetus has followed a tortuous h. The increased sensitivity of off pring to the hemorrhagic of the active principle of damaged sweet clover wa served more than 50 years ago and hemorrhagic compli a in human newborns resulted in general recommenda that these agents (including Coumadin [Endo Laborato] shouldn t be used in the latter part of the third trimester pregnancy

n the last five years we and others have demonstrated coumarin derivative exposure in the first trimester of results in a specific malformation syndrome in infants which has come to be known as the warfarin bryopathy We are aware of 39 infants with the warfarin nbryopathy which is characterized by nasal hypoplasia and ippled epiphyses Review of exposure histories in these ca es cates that there is a critical period of exposure between six d nine weeks of gestation that can result in the appearance the warfarin embryopathy The severity of this syndrome is riable follow up studies indicate that while seven subjects ve died most survivors have a relatively good outlook with lf having no severe disability at all.

Our recent review also summarizes experience with central rvous system effects of coumarin derivative exposure in ero Administration of these agents in the second and third mester appears to be associated with deformation of the ntral nervous system resulting in mental retardation and/ blindness A total of 15 such cases were found While some ildren have had both the embryopathy and central nervous stem abnormalities these appear to be two independent ocesses with different sensitive periods during gestation fferent mechanisms of pathogenesis and with independent additive risks

So coumarin derivative exposure in the sixth to ninth weeks the first trimester carries some risk for the warfarin ryopathy exposure in the second and/or third trimesters with increased incidence of central nervous stem abnormalities and late third trimester exposure carries with it a clearly recognized danger of late prenatal, perinatal or postnatal hemorrhage

Nevertheless use of anticoagulants during pregnancy may be necessary because of maternal thrombophlebitis with embolization or maternal prosthetic heart valves. Counseling of such women requires estimation of the involved risks The most satisfactory approach would be a prospective controlled trial but no such trial has been undertaken and since the coumarin derivatives are now contraindicated during pregnancy by their manufacturers none will probably be forthcoming Yet some estimate needs to be available After an unsuccessful attempt to retrospectively ascertain all women given anticoagulants during pregnancy in the Seattle Washington area over the past ten years, we chose to review the world s literature from 1945 through 19 8 attempting to find all published cases of courmarin derivative (and for comparison heparin) use during pregnancy The limitations and bias of such a study should be evident therefore our risk figures must be considered as *estimates* For coumarin derivatives 418 literature cases were reviewed Over all only two thirds of these pregnancies resulted in reasonably normal fetal outcome Abnormalities in the others were primarily secondary to hemorrhage warfarin embryopathy central nervous system effects and spontaneous abortion. In at risk pregnancies (exposure between six and nine week of gestation) about 8% of infants were reported to have features of the embryopathy The over all risk of central nervous system effects appears to be about 3% Of liveborn infants 16% had some significant sequelae So the best available estimates indicate that with coumarin derivative use one sixth of pregnancies will result in abnormal liveborn infants, one-sixth will end in abortion or stillbirth and about two-thirds will have a relatively normal outcome

Data from 135 published cases in which heparin was used during pregnancy indicate a virtually identical complication rate less than two-thirds of such pregnancies resulted in normal children The kinds of problems, however were quite different heparin use was associated for the most part with

80/110761 + 02$00 20/0 © 1980 The C V Mosby Co

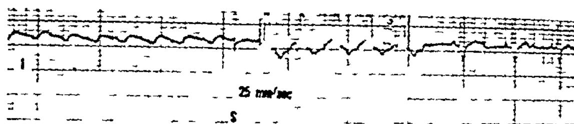


Fig 1 Ventricular tachycardia with a rate of 140 per minute terminated after six ventricular stimulations at a rate of 110 per minute

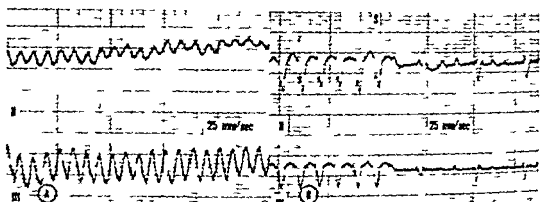


Fig 2 Simultaneous recording of Leads II and III A ventricular flutter with a rate of 260 per minute B ventricular stimulation at 200 stimuli per minute and then sinus rhythm with A V block.

interrupted the reentry circuit, allowing the others to drive the atrium, and after the last stimulus sinus rhythm occurred.

The same mechanism was observed in a 70-year-old woman with total A V block and bursts of ventricular tachycardia and ventricular flutter uninfluenced by repeated DC shocks. The ventricular stimulation below the rate of ventricular tachycardia (Fig 1) and below the rate of ventricular flutter (Fig 2) succeeded in driving the ventricles and finally in stopping the arrhythmia A permanent ventricular pacemaker was effective in preventing these arrhythmias and the patient was in satisfactory condition at a follow up examination 3 months later

Simion Cotoi
Alexandru Incze
Constantin Georgescu
Emilian Carasca
First Medical Clinic
(Director Prof Dr C Dudea)
4300 Tirgu Mureş
Romania

REFERENCES

1 Batchelder J E and Zipes, D P Treatment of tachyarrhythmias by pacing Arch. Intern Med. 135 1115 1975
2 Cotoi, S Georgescu, C and Cozlea P Retrograde Wenckebach phenomenon in ventricular tachycardia AM. HEART J 95 676 1978
3 Cotoi, S Georgescu, C Incze A. and Cozlea P Termination of atrial flutter by atrial pacing demonstrated through intracavitary recordings, Rev Roum Med. Med. Int 17 257 1979
4 Denes, P., Wu D Dhingra, R C Amat Y Leon Wyndham, C., Mautner R. K., and Rosen, K. Electrophysiological studies in patients with chr recurrent ventricular tachycardia, Circulation 54 1976
5 Fisch, C., and Noble R J Ventricular tachycardia. HEART J 89 551 1975
6 Fisher J D., Cohen H L., Mehra R., Altschuler Escher D J W., and Furman, S Cardiac pacing pacemakers. II Serial electrophysiologic pharmaco testing for control of recurrent tachyarrhythmias HEART J 93 658 1977
7 Hartzer G O., and Maloney J.D Programmed ventr ular stimulation in management of recurrent ventri tachycardia, Mayo Clin. Proc 52 731 1977
8. Lurie A. J., Salel, A. F., Vera, Z., DeMaria, A. N. Hu E J., and Mason, D T Rapid overdrive pacing refractory tachyarrhythmias in patients after open-he surgery J Thorac Cardiovasc Surg 72 458 1976
9 Wellens H.J J Schulenburg R.M and Durrer D. Electrical stimulation of the heart in patients v ventricular tachycardia Circulation 53 1 6 1976

TTM versus Holter monitoring of symptomatic arrhythmias

To the Editor

In their article in the October 1979 issue of the Journ (AM HEART J 98 459 1979) Dr R S Grodman and as ciates pointed out that the value of a patient activated EC telephonic transmission system (TTM) was statistically s

ic electrocardiographic recording ring sexual activity in recent post myocardial and revascularization patients

the Editor

We greatly appreciated the article of Johnston and Fletcher hich appeared in the December 1979 issue of the AMERICAN HEART JOURNAL, and we would like to make some comment it.

At the moment in our Cardiac Rehabilitation Center we focused our attention only on post myocardial infarction atients (post MI Pts)

Sixty nine post MI Pts, 26 randomly assigned to a physical 27 to a control group and 16 excluded randomization for cardiovascular contraindications, per 85 24 hour ambulatory electrocardiograms during hich there were 86 occurrences of sexual intercourse

The time lapse from MI was 49 6 ± 10.3 days, ages, ranged 30 to 64 years (x̄ = 49) the infarction was inferoposterior 41 and anterior in 28 patients.

Total time for sexual activity ranged from 8 to 28 minutes = 16.5) and we included in the analysis 10 minutes before 10 minutes *after that event peak heart rate ranged from* 170 beats per minute (x̄ = 106)

Ventricular ectopic activity (VEA) was graded according to Lown system integrated with a study of bi tri and and has been expressed as percent of hours certain degree of VEA. A total of 1 092 daily hours 86 instances of sexual intercourse have been reviewed eeping hours have not been included. Total VEA and ultiform extrasystoles were increased although not signifi during sexual activity (SA) The most striking differ regarded the advanced grades of VEA, namely couplets, and bi, tri and quadrigeminy that all significantly more frequent during SA ($P < 0.025$)

A further analysis comparing sex with other daily activities as driving, climbing stairs, light manual work, prandial post prandial state awakening etc., showed that though SA elicited more advanced grades of VEA the fference was not statistically significant.

In our total population of 263 patients under study we have ot observed any "mort d amour" In conclusion, in our xperience sexual activity in the early post hospital phase of II is not clearly a stronger stimulus than are other activities r cardiac electric instability Even if we agree that appro counseling should obviously be expressed regarding ivity in this phase of patient management excessive seems to be inappropriate and may create psycholog problems.

Vito Paolillo M.D
Sebastiano Marra M.D
Felice Spadaccini M.D
Pier Federico Angelino M.D
Cardiac Rehabilitation Centre
Division of Cardiology
Ospedale Maggiore di S Giovanni Battista
e della Città di Torino
Turin Italy

REFERENCES

1 Johnston B L., and Fletcher G F. Dynamic electrocardiographic recording during sexual activity in recent post myocardial infarction and revascularization patients, AM HEART J 98 736 1979
2. Paolillo V Marra, S., Spadaccini, F., Chiappa, E., Boncompagni, F., Oddenino G., and Angelino P F Variazioni giornaliere dell attività ectopica ventricolare in pazienti con infarto miocardioco recente Giorn. It. Cardiol. (In press)

Reply

To the Editor

We appreciate the interest shown in our study by Drs. Paolillo and associates. It appears as though both groups of data are quite comparable However Paolillo and co-workers studied only patients with myocardial infarction and at a time of *49 6* days post infarction Our myocardial infarction patients were monitored at an *earlier* mean time of *30 1* days post infarction This earlier "time frame" for monitoring *could possibly account for the fact that one myocardial* infarction patient experienced ventricular bigeminy and ventricular coupling during sexual activity and not during other activities within his 24 hours. However the higher grades of ventricular ectopic activity (VEA) detected by Paolillo and colleagues, even at a later time post myocardial infarction, should be of concern We concur that counseling should not be such as to incite "alarm" in the patient and partner However the apparent relationship between the incidence of sudden death and high grade VEA in patients with ischemic heart disease does warrant consideration of therapeutic approaches that are tailored for the benefit of the individual subject in question.

Barbara Johnston, M.N
Gerald F Fletcher M.D
Georgia Baptist Medical Center
300 Boulevard N.E
Atlanta Ga 30312

REFERENCE

1 Coronary Drug Project Research Group Prognostic importance of premature beats following myocardial infarction, J.A.M.A. 223 1116, 1973.

Pacing below the ventricular rate in terminating ventricular tachycardia and flutter

To the Editor

Short bursts of ventricular stimuli at about 200 per minute or programmed ventricular premature beats, allowed termination of medically refractory recurrent ventricular tachycardias. [1-4]

In a former paper on atrial flutter using a stimulation below the atrial rate we have found that the first stimulus

exist a small group of patients whose infrequency and short duration of symptoms will defy ECG documentation by the above methods i e the white field of Weber and associates Perhaps this group of patients is better studied by a long term limited usage patient actuated Holter type recording system as a further adjunct to standard H.M and T T M

Richard S Grodman M D
Director Non Invasive Laboratory
St Vincent's Medical Center
of Richmond
New York N Y 10301
Robert J Capone M D
Associate Professor of Medicine
Brown University
Director Coronary Care
Rhode Island Hospital
Albert S Most M D
Associate Professor of Medicine
Brown University
Physician in Charge
Division of Cardiology
Rhode Island Hospital
Providence R I 02902

REFERENCES

1 Hasin Y David D., and Rogel S Diagnostic and therapeutic assessment by telephone electrocardiographic monitoring of ambulatory patients Br Med J 2 609 1976
2 Judson P Holmes D R and Baker W P Evaluation of outpatient arrhythmias utilizing transtelephonic monitoring Am Heart J 97 759 1979

Ratios of septum and LV free wall in IHSS and HCM

To the Editor

Idiopathic hypertrophic subaortic stenosis or hypertrophic cardiomyopathy is characterized by asymmetric septal hypertrophy (ASH) myocardial fiber disarray and often systolic anterior motion of the mitral valve (SAM) Although these findings are highly suggestive however none of them are pathognomonic for this fascinating disorder ASH (a ratio of the septum to posterior left ventricular free wall of ≥ 1 3) has been reported in normal embryonic and newborn hearts as well as in certain congenital heart disorders While studying embryonic chicken hearts for a teratologic project we conducted a (quantitative) morphometric investigation on three groups of white Leghorn chicken hearts (8 day old embryos 1-day old chickens and adult specimens) Serial sections parallel to the frontal plane were obtained from 10 hearts in each group and were stained with hematoxylin and eosin Sections containing the ventricular septum medial leaflet of the mitral valve and the aortic root were used for morphometric study (Fig 1) A line *(A)* was drawn parallel to the longitudinal axis of the ventricular septum Perpendicular lines were dropped to line A at three points (dividing line A into four equal portions) and were extended laterally to cross the left ventricular free wall The length of the line A was determined by the aortic root *(Y)* superiorly and its point of intersection (X) with line B passing tangentially to the

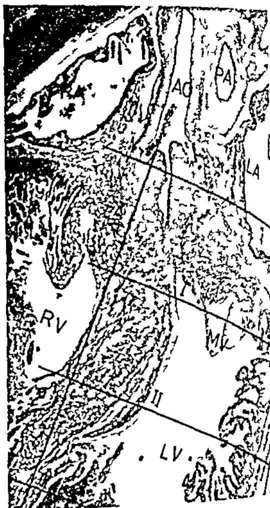


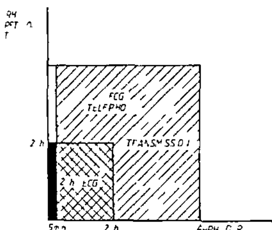
Fig 1 A typical frontal section of chicken heart contain[ing] the aortic root *(AO)* the medial cusp of the mitral val[ve] *(MV)* and lines drawn for measuring septal to left ventricu[lar] wall thickness ratio at three equidistant levels *(I II* and *III)* Line B is not shown in the Figure *LA* = left atriu[m] *LV* = left ventricle *PA* = pulmonary artery *RA* r[ight] atrium *RV* = right ventricle

lowermost part of the left ventricular wall. Ratios of t[he] septal thickness to the left ventricular wall were measured [at] three levels for the three groups and were compared using [t]... hypothesis on mean ± SD of each group (Table I) The st[atistical analysis] showed that

1 The ratio for the upper portion *(level I)* of the septum [to] left ventricular free wall is quite large in the embryonic [heart] and this ratio is rapidly reduced so that in 1-day-old chick[ens] the upper ratio has reached the adult level and does [not] change further with advancing age

2 The ratio for the middle portion *(level II)* declines [more] gradually so that in 1 day old chickens it is not signific[antly] less than in the 8-day-old embryos however as the chick[ens] mature this ratio is gradually reduced and becomes sig[nifi]cantly smaller in the adult specimens.

3 The ratio for the lower portion *(level III)* though redu[ced] with advancing age is not significantly different among [the] three groups



g 1 Diagram illustrating the overlapping coverage of mptomatic arrhythmias provided by the use of *both* TTM nd 24 hour Holter monitoring Short lasting symptomatic rrhythmias (< 5 min i e mean TTM-connection time) of igh reoccurrence frequency (> one phenomenon/day) could nly be captured using HT *(pure black field)* whereas rare rrhythmias (< 1/day) will remain undiscovered in spite of ne aplication of both methods used *(pure white field)*

ificantly higher (χ = 3 69 p < 0 05) than the analysis of one 4 hour Holter tape (HT)

But the truth is that each method brings different strengths o the problem of capturing symptomatic arrhythmias

It is important to understand that the sensitivity of HT and M depends on the frequency of the occurrence of symptoms vs. arrhythmias In 9? symptomatic patients—in spite of mean 4 days (maximum 21 days) continuous monitoring ime under ambulatory conditions—a symptom/ECG correla ion could be achieved in only 40 patients Using computer upported HT analysis sytems the analysis of synchronous egistration of ECG and symptoms leads to the true result ndependent of the duration of the phenomenon

On the other hand a successful application of TTM (i.e a imultaneous ECG registration of a symptomatic period) resupposes that there will be a telephone connection between he patient and the receiving unit *before* the symptoms anish.

So we conclude that the value of HT analysis depends on he *frequency* whereas the value of TTM is a function of the *duration* of symptoms vs arrhythmias A disregard of the luration and frequency of symptoms shows a lack of under tanding of the value of each method

Both methods are useful tools with which to reduce the white field (see Fig 1) of undiscovered symptomatic arrhyth mias by the use of overlapping data

Univ Asst H Weber M.D
Univ Doz K Steinbach M.D
Univ Asst G Joskowicz M Ph
Univ Asst D Glogar M.D
Univ Prof K Kaindl M.D
Kardiologische Universitats Klinik
Vienna
Austria

REFERENCES

1 Grodman, R S Capone R J., and Most A S Arrhythmia surveillance by transtelephonic monitoring Comparison with Holter monitoring in symptomatic ambulatory patients AM HEART J 98 459 1979
2 Abdon N J Lecerof H and Johansson B E Electrophysiological examination or monitoring in suspected Adams Stokes syndrome? PACE 2 94 1980
3 Joskowicz, G., Balatka H., Glogar D., Weber H and Steinbach K A high speed digital Holter tape analysis with full editing capability Computers in Cardiology Geneva 19 9 p 277
4 Weber H Glogar D Joskowicz G., Pfundner P., and Steinbach K. Application of trans-telephone monitoring and arrhythmias Telemetry of the Cardiovascular System Symposium, Erlangen 1979 in press.

Reply

To the Editor

We thank Drs Weber Steinbach, Joskowicz, Glogar and Kaindl for their interest in our article We agreed that the sensitivity of Holter monitoring (H.M) and transtelephonic monitoring (T T M) is a function of the frequency and duration of symptoms and arrhythmias.

The efficacy of H M is truly limited by the frequency of the patient s symptoms it is less likely to document symptom related arrhythmias in the sporadic patient than in the highly ymptomatic patient. This is exactly the reason we sought to test T T M as an alternative to H.M in this situation. T T.M., on the other hand is duration limited i e. an arrhythmia must be present at the time of the transtelephonic transmission in order to be documented In addition a sustained critical arrhythmia may render the patient incapable of transtelephonic transmission thereby losing the opportunity for symptom ECG correlation We have recognized these conditions and listed them in our discussion as did Hasin and colleagues and Judson and co-workers in their studies on the usage of T T.M

We believe it is important when correlating symptoms with the transmitted ECG to have the patient relate by telephone whether or not symptoms were actually occurring *during* the period of ECG transmission This will eliminate one source of symptom ECG disparity Also by extending the time period for the use of T T M., it will be more likely that a truly symptomatic period can be recorded further improving the sensitivity of the method.

Weber and associates note that a period of continuous ECG ambulatory monitoring of 4 days (mean) duration, with a maximum continuous recording period of 21 days, can achieve a high incidence of recording during symptoms, and a high symptom ECG correlation This frequent application of continuous recording is appropriate for investigative purposes, but is neither practical nor possible in the routine care of patients. Thus effective therapeutic efforts must depend on either a single or perhaps two 24 hour Holter recordings or must seek other techniques for documentation of the patient s ECG at the time of potential cardiac symptoms. We believe that the T T.M has emerged as one method of achieving this goal

Finally we stated that T T.M both complements and supplements H.M in symptomatic patients. There still will

We note also that Case 2 was not described as having an abnormal mean frontal QRS axis on the electrocardiogram whereas five of the six patient described by Ehlers and associates had a superiorly orientated axis, and this has also been our experience (Duncan W J., unpublished observations) Is there any further evidence not mentioned in the article that might suggest that Case 2 does in fact have eccentric left ventricular hypertrophy rather than an aneurysm?

J E Burns
J A G Culham
W J Duncan
From the Division of Cardiology of the Department of Pediatrics and the Department of Radiology
Hospital for Sick Children
Toronto Ontario Canada

REFERENCES

1 Singh, A., Katkov H., Zavoral, J H., Sane S M., and McLeod J D Congenital aneurysms of the left ventricle AM HEART J 99 2, 1980
2 Ehlers, K. H., Engle M A., Levin A. R., and Deely W J Eccentric ventricular hypertrophy in familial and sporadic instances of 46 XX XY Turner phenotype Circulation 45 639 1972

Reply

To the Editor

We appreciate the comments of Dr Burns and colleagues regarding Case No 2 in our recent communication Our Case No 2 did not demonstrate the electrocardiographic abnormalities seen by Ehlers and associates in patients with eccentric left ventricular hypertrophy The mean frontal QRS axis was +30 degrees and there was normal progression of the R wave in all precordial leads. Furthermore an echocardiogram obtained at the age of 13 years when the patient weighed 95 pounds demonstrated the thickness of the interventricular septum as well as the left ventricular posterior wall to be 8 mm. A chromosomal analysis has not been done but the patient has no abnormal features to suggest any syndrome Therefore we feel that this case demonstrates a left ventricular aneurysm rather than eccentric left ventricular hypertrophy of the left ventricule

Amarjit Singh M D
Minneapolis Medical Center
Childrens Health Center
2525 Chicago Ave South
Minneapolis Minn. 55404

REFERENCES

1 Singh, A. Katkov H. Zavoral J H., Sane S M., and McLeod J D Congenital aneurysms of the left ventricle AM HEART J 99 2, 1980
2. Ehlers K H Engle M A Levin A R. and Deely W J Eccentric ventricular hypertrophy in familial and sporadic instances of 46 XX, XY Turner phenotype Circulation 45 639 1972

Anomalous ECG and PCG recordings

To the Editor

In the article by Drs. Lofty L. Basta and Jerry J Ber... (AM HEART J 97 96 1979) on page 108, in Fig 13, the left parasternal cardiogram and the phonocardiogram seem to have some mistakes. If the figure is placed correctly points E in the parasternal cardiogram and S_1 in the phonocardiogram are labeled incorrectly because each of them precedes the QRS complex in the ECG On the other hand, the S_1-S_2 interval being longer than the S_2-S_1 interval is peculiar

I think that this figure should be placed upside down; then one could see the positive P wave with a P R interval of 0.2 sec. in the ECG the S_1-S_2 greater than S_2-S_1 and the form S_1 in the PCG and point E after the QRS and a large systolic positive outward movement in the parasternal cardiogram.

I would appreciate it very much if you could reevaluate this matter

Türkan Gurel, MD
Department of Cardiology
Ankara University
School of Medicine
Ankara Turkey

Reply

To the Editor

The authors appreciate Dr Gurel s comments and can clearly see Dr Gurel s point

However this particular recording is obtained from a patient with left bundle branch block and marked intraventricular conduction delay The initial part of the QRS is not seen in the ECG lead recorded. *In fact*, it was about 0.08 sec earlier than the first upward deflection seen in this particular lead Furthermore we believe S_1 in this figure is the tricuspid component of the first heart sound recorded in the left parasternal area whereas the S_2 is the aortic component of the second heart sound which is considerably delayed in this case because of *left bundle branch block*, accounting for the long S_1-S_2 interval.

Lofty L. Basta M.D F.A.C.C.
F.A.C.P M.R.C.P M.R.C.P.
Clinical Director of Cardiology
St. John s Medical Center
Clinical Professor of Medicine
Divisional Director of Cardiology
Tulsa Medical College
St John s Doctors Building
Suite ...
1 05 E 18th S.
Tulsa Okla. ...

able I Mean values and SD of septal/left ventricular free wall thickness ratios at three levels or the three groups of hearts

	Level 1	*Level 2*	*Level 3*
Group I			
8-day-old embryos	1.6144 ± 0.516	1.3560 ± 0.252	1.1440 ± 0.163
Group II			
1-day old chickens	1.0625 ± 0.143	1.[illegible]0 ± 0.260	1.2400 ± 0.347
Group III			
adult hearts	1.0590 ± 0.129	0.946 ± 0.133	0.9[illegible]66 ± 0.240
p values			
I vs III	< 0.01	< 0.001	NS
I vs II	< 0.01	NS	NS
II vs III	NS	< 0.01	NS

S = not significant

As the septal to left ventricular free wall ratio may be duced by septal thinning or left ventricular free wall uckening it may be stated that either the ventricular ptum thins out rapidly at the upper level more slowly at ud level and not at all at the lower level or the left ntricular free wall thickens more rapidly at the upper level iore slowly at the mid level, and not at all at the lower level tudies are in progress aimed at answering this question in iore detail however preliminary evaluation of results shows hat both factors are simultaneously operative

Jami G Shakibi MD FACC
Fatemeh Reyhani DVM
Iraj Naranan MD FCAP
From the Departments of
Pediatric Cardiology
Experimental Medicine and Pathology
The Cardiovascular Medical and
Research Center
Heart Hospital (Rezai)
PO Box 33 423
Tehran Iran

EFERENCES

1 Henry W L, Clark, C E and Epstein S E Asymmetric septal hypertrophy (ASH) echocardiographic identification of the pathognomonic anatomic abnormality of IHSS Circulation 47 225 1973
2 Maron B J and Roberts, W C Quantitative analysis of cardiac mus le cell disorganization in the ventricular septum of patients with hypertrophic cardiomyopathy Circulation 59 689 1979
3 Epstein S E Henry W L Clark C E et al Asymmetric septal hypertrophy Ann Intern Med 81 650 1974
4 Maron B J Edwards J E Moller J H and Epstein S E Prevalence and characteristics of disproportionate ventricular septal thickening in infants with congenital heart disease Circulation 59 176 1979
5 Maron B J Gottdiener J S Roberts W C et al Nongenetically transmitted disproportional ventricular septal thickening associated with left ventricular outflow obstruction Br Heart J 47 345 1979
6 Maron B J Verter J and Kapur S Disproportionate ventricular septal thickening in the developing normal human heart Circulation 57 520 1978



Fig 1 Left ventricular angiogram in diastole of a patient with eccentric left ventricular hypertrophy

LV hypertrophy versus aneurysm?

To the Editor

We enjoyed the article "Congenital aneurysms of the left ventricle" by Dr Singh and associates and we have one important question to raise. In the angiograms shown by Dr Singh and colleagues, we agree that three of the four cases showed convincing aneurysms of the left ventricle With regard to Case 2 however we were struck by the resemblance of the left ventricular outline to that seen in eccentric left ventricular hypertrophy as described by Ehlers and coworkers. We also have seen this particularly in patients with Noonan s syndrome We include a diastolic frame from such a left ventricular angiogram (Fig 1) to show the similarities. In systole the apical segment did not contract paradoxically

We note also that Case 2 was not described as having an abnormal mean frontal QRS axis on the electrocardiogram whereas five of the six patient described by Ehlers and associates[2] had a superiorly orientated axis and this has also been our experience (Duncan W J., unpublished observations) Is there any further evidence not mentioned in the article that might suggest that Case 2 does in fact have eccentric left ventricular hypertrophy rather than an aneurysm?

J E Burns
J A G Culham
W J Duncan
From the Division of Cardiology of the Department of Pediatrics and the Department of Radiology Hospital for Sick Children Toronto Ontario Canada

REFERENCES

1. Singh, A., Katkov H., Zavoral, J H., Sane S M., and McLeod J D Congenital aneurysms of the left ventricle AM HEART J 99 25 1980
2. Ehlers, K. H., Engle M A., Levin A R., and Deely W J Eccentric ventricular hypertrophy in familial and sporadic instances of 46 XX XY Turner phenotype Circulation 45 639 1972.

Reply

To the Editor

We appreciate the comments of Dr Burns and colleagues regarding Case No 2 in our recent communication. Our Case No 2 did not demonstrate the electrocardiographic abnormalities seen by Ehlers and associates in patients with eccentric left ventricular hypertrophy The mean frontal QRS axis was +30 degrees and there was normal progression of the R wave in all precordial leads Furthermore an echocardiogram obtained at the age of 13 years when the patient weighed 95 pounds demonstrated the thickness of the interventricular septum as well as the left ventricular posterior wall to be 8 mm A chromosomal analysis has not been done but the patient has no abnormal features to suggest any syndrome Therefore we feel that this case demonstrates a left ventricular aneurysm rather than eccentric left ventricular hypertrophy of the left ventricule

Amarjit Singh M.D
Minneapolis Medical Center
Childrens Health Center
2525 Chicago Ave South
Minneapolis Minn 55404

REFERENCES

1. Singh, A. Katkov H Zavoral J H., Sane S M., and McLeod, J D Congenital aneurysms of the left ventricle AM HEART J 99 25 1980
2. Ehlers K. H Engle M A Levin A. R., and Deely W J Eccentric ventricular hypertrophy in familial and sporadic instances of 46 XX XY Turner phenotype Circulation 45 639 1972

Anomalous ECG and PCG recordings

To the Editor

In the article by Drs Lofty L. Basta and Jerry J Be[illegible] (AM HEART J 97 96 1979) on page 108 in Fig. 18, the le[illegible] parasternal cardiogram and the phonocardiogram seem to have some mistakes. If the figure is placed correctly pr[illegible] in the parasternal cardiogram and S in the phonocardiogram are labeled incorrectly because each of them precedes the QRS complex in the ECG On the other hand, the S-S interval being longer than the S S interval is peculiar

I think that this figure should be placed upside down, th[illegible] one could see the positive P wave with a P R interval of 0.1[illegible] sec in the PCG the S S greater than S-S and the first in the ECG and point E after the QRS and a huge [illegible] positive outward movement in the parasternal cardiogram.

I would appreciate it very much if you could reevaluate this matter

Turkan Gurel, M[illegible]
Department of Cardi[illegible]
Ankara Univers[illegible]
School of Medici[illegible]
Ankara, Turk[illegible]

Reply

To the Editor

The authors appreciate Dr Gurel s comments and c[illegible] clearly see Dr Gurel s point.

However this particular recording is obtained from [illegible] patient with left bundle branch block and marked in[illegible] tricular conduction delay The initial part of the QRS [illegible] seen in the ECG lead recorded. In fact it was about 0.0[illegible] earlier than the first upward deflection seen in the para[illegible] lead Furthermore we believe S in this figure is the tr[illegible] component of the first heart sound recorded in the l[illegible] parasternal area whereas the S_1 is the aortic component of [illegible] second heart sound which is considerably delayed in th[illegible] because of left bundle branch block, accounting for the l[illegible] S -S interval.

Lofty L. Basta M.D F.AC[illegible]
F.A C.P M R C.P M.R C.P[illegible]
Clinical Director of Cardi[illegible]
St John s Medical Ce[illegible]
Clinical Professor of Med[illegible]
Divisional Director of Card[illegible]
Tulsa Medical C[illegible]
St John s Doctors Bu[illegible]
Suite [illegible]
1705 E 19[illegible]
Tulsa Okla. [illegible]

ook reviews

rdiac Rehabilitation for the Practicing Phys cian Edited Lenore R Zohman M D and Albert A Kattus M D St uis 19 9 The C V Mosby Company 124 pages

This is a 1?4 pa e book on a subject which is relatively poLr in cardiology All physicians responsible for patients th heart disease are primarily responsible for rehabilita n of their patient This book reviews briefly the concepts in actice today The nine parts include general discussions ychological considerations, work and job rehabilitation and b placement exercise programs, risk factors sexual activity d other aspects of rehabilitation of patients with myocar al infarction The many contributors express their views early and effectively This is the second volume of a series of lumes under the editorship of Dr Zohman These papers re presented at a symposium held during March 19 ysicians in practice will find these discussions to be useful d interesting especially if they have never considered rdiac rehabilitation seriously The increasing interest in this bject makes this publication important It is practical and is rected at the busy practicing clinician with little time for udy

ercise Electrocardiography Practical Approach Edited by dward K Chung M D F.A.C.C Baltimore 1979 The illiams & Wilkins Company 354 pages Price $30 00

This book on exercise testing electrocardiography edited by r Chung and 13 contributors reviews exercise testing tech ques and principles The problems related to the use of ercise testing are discussed Indications contraindications erpretation of data values in screening for heart disease nd complications are among the subjects discussed B cause f the use of exercise testing physicians who use and rely on his procedure in clinical practice will find this book interest g and especially useful for physicians in training The lus rations are good and the presentations of bibliographies re helpful This is not a book in which to find a concise ri cal discussion of the need for exercise testing dangers alue and limitations of exercise testing Nevertheless the use nd practices at present are described The reader will have to ecide for himself as to the usefulness of the book to him

Venous & Arterial Thrombosis Edited by J Heinrich Joist I D Ph D and Laurence A Sherman M.D New York 979 Grune & Stratton Inc 373 pages Price $18 50

This is a new publication on an old important clinical roblem It represents a series of reports from a symposium eld on April 6 and 7 19/8 The contributions include among he many a pects of thrombosis pathogenesis diagnosis, ulmonary embolism prevention mechanism of action of eparin and coumadin role of thrombolytic therapy myocar ial infarction cerebrovascular occlusive disease use of radioi otopic detection and platelet suppressant therapy This ublication provides a good single source on the subject of hrombosis It includes current concepts and interests It is a useful book for clinicians surely for cardiologists

Advances in Microcirculation The Microcirculation in Diabetes Edited by E Davis with B M Altura and H Harders Basel 19 9 S Karger AG 15? pages Price $81 00

This is volume 8 of *Advances in Microcirculation* Changes n the small vessels in diabetes though known to exist for many years remain a great puzzle in medicine This impor ant publication of 15? pages is extremely interesting Among the subjects discussed are hemorrheology basal lamina in capillaries, mana ement of leg ischemia and vascular smooth muscle The discussions are concerned with pathogenesis pathology and clinical diagnosis and management The rela tionship of diabetes to the vascular lesions is discussed effectively This is another important and timely volume on the microcirculation

Current Cardiology vol 1 Edited by M Irene Ferrer M D Boston 1979 Houghton Mifflin Company 384 pages Price $30 00

This is *Volume 1* of *Current Cardiology* the series to be edited by Dr Ferrer The purpose of these annual volumes is to make available the chan es in cardiology to the practicing physician and cardiologi t as they occur ea h year The 1? chapters in this volume include a discussion of hypertension valvular heart disease coronary artery disease pediatric cardiology ventricular function arrhythmias pacemakers the cardiac cell echocardiography cardiac surgery cardiovas cular pathology and other subjects The presentations are too brief to be comprehensive enough to inform the reader adequately of the subjects selected for discussion Some of these problems selected are complex and currently there are differences of opinion concerning the mechanism and patho physiology in olved and they need future study This is well exemplified by the chapter on the use of vasodilators for CHF Starling s law of the heart the role of the peripheral circula tion and the nervous system is too extensive a field to discuss in about 11 pages This is also true for the broad field of cardiovascular pathology whi h is presented in less than 20 pages Regardless the discussions are interesting and present current views in cardiology These vie vs are discussed in a critical manner It is hoped in future volumes that either fewer subjects are selected for more thorough and critical review or that the subjects selected be more specific There is a need for critical evaluation and review and discussion for the read r of current practices and concepts in cardiology This is especially important for the reader who is less informed and trained and who needs a critical evaluation of current concepts and practices in cardiology

Hemodynamics and the Blood Vessel Wall Edited by William E Stehbens, M D., Sprin field Ill. 19/9 Charles C Thomas, Publisher 646 pages Price $68.50

This is an important book Hydraulic engineers have devel oped the fundamental principles of fluid flowing through rigid tubes, whereas blood vessels are not rigid and blood is a non Newtonian fluid The hydraulic principles governing the flow of blood through small and large blood vessels depend upon different factors related to the elasticity of the wall the distensibility of the vessels the changing tone and other complex factors These and many other hemodynamic and physiologic phenomena are discussed by the several contribu tors. Blood flow in vessels in association with certain disease states such as aortic stenosis, aneurysms A V shunts and arterio clerosis are discussed

Stehbens a pathologist has nicely related morphologic normal, and pathologic tates to hemodynamic phenomena The book is a good one which should interest pathologists and physiologists. It is unlikely that practicing physicians will appreciate the book fully There has been a need to describe in a single volume for the convenience of others the relationship of the physiologic and morphologic characteristics of hemody namic phenomena.

Fourth Annual National Symposium on Aging

The Fourth Annual National Symposium on Aging will be held on November 15 and 16 1980 at the Golden Gateway Holiday Inn San Francisco Devoted to a review of health care needs of the elderly sessions will center on a description of health care for older people and a review of the resources available Specific and prevalent problems in geriatric medicine will be examined such as the aging heart stroke and the older patient cancer and aging and depression and disengagement among the elderly Ultimately the recommendations of this symposium will be included in the 1981 White House Conference Fee for the symposium is $90 and AMA credit is available For further information contact Continuing Education in Health Sciences University of California San Francisco 24 Kirkham San Francisco Calif 94143 Telephone (415) 666 3904

Clinical Recognition and Management of Heart Disease 1981

The 24th Annual Scientific Session of the American Heart Association, Arizona Affiliate will be held on January 21 through 24 1981 at the University of Arizona Health Sciences Center Tucson The seminar is entitled "Clinical Recognition and Management of Heart Disease 1981 Visiting faculty will include Robert S Eliot M D., University of Nebraska Michael S Gordon M D Ph D F A C P University of Miami School of Medicine Donald C Harrison M D., Stanford University and Douglas P Zipes, M D., Indiana University Emphasis will be placed on bedside observation and auscultatory skills stressed through the use of the Cardiac Patient Simulator The lectures will deal with the management of cardiovascular problems with special reference to new pharmacologic approaches and modes of therapy Comprehensive audiovisual presentations are planned and the course has been structured to permit participants to explore areas of individual interest in depth.

For further information write Gordon A Ewy M D Professor of Medicine Course Co-Director Dept of Internal Medicine Section of Cardiology Health Sciences Center University of Arizona Tucson Ariz 85724

Society for Clinical Trials Symposium

A Combined Annual Scientific Sessions of the Society for Clinical Trials and the Eighth Annual Symposium for Coordinating Clinical Trials will be held May 11 through 13 1981 in San Francisco California Sessions will focus on the design organization management and analyses of clinical trials Abstracts must be received by January 1 1981 For further information write Christian R Klimt M D Secretary Society for Clinical Trials Inc 600 Wyndhurst Ave Baltimore Md 21210

Lucien Dautrebande Pathophysiology Prize–1982

The "Foundation de Physiopathologie Professeur Lucien Dautrebande" will hold its next competition for the Dautrebande Prize in 1982 and the award will be approximately 1 400 000 Belgian francs. The award will be given for a work in human or animal clinical physiopathology preferably having therapeutic implications. For further information about the competition please write Office Fondation de Physiopathologie Professeur Lucien Dautrebande 35 chaussée de Liège 5200 Huy Belgium For consideration in the 1982 competition all papers must be received *before* December 31 1981.

Second Banff Hypoxia Symposium

The Second Banff Hypoxia Symposium sponsored by The Arctic Institute of North America will be held at the Banff Springs Hotel, Banff Alberta Canada on January 13 through 17 1981 The program is designed to interest clinicians and research workers a special session on January 17 will be devoted to the diagnosis management and prevention of altitude illness Registration for the four-day symposium is $150 or $120 if paid by December 1 1980 A maximum of [illegible] persons will be accepted For further information contact John R Sutton M D The Arctic Institute of North America The University of Calgary 2500 University Drive NW The University of Calgary Calgary Alberta Canada T2N 1N4 Telephone [illegible] 3387

Conference on Coronary Artery Bypass Surgery

The National Heart Lung and Blood Institute (NHLBI) in collaboration with the Office for Medical Applications of Research (OMAR) National Institutes of Health, and the National Center for Health Care Technology (NCHCT) are sponsoring a Consensus Development Conference on Coronary Artery Bypass Surgery to be held on December 3 through 5 1980 at the National Institutes of Health Bethesda Md. The conference will focus on the clinical and scientific aspects of coronary artery bypass surgery A second conference emphasizing the economic societal and ethical aspects of the procedure will be sponsored in Spring 1981 by the NCHCT with the collaboration of NHLBI and OMAR For further information regarding the December conference contact Nancie McManus, Prospect Associates, 11325 Seven Locks Rd., Potomac MD 20854 Telephone (301) 983-[illegible]

›ks received

ng EKG's in Infants and Children By J A Harris A. R Feinstein Boston 1979 Little Brown & Company pages Price $12.50

Heart Valves By Marian I Ionescu M D F.A C S Mass. 1979 Butterworths, USA 373 pa es. Price 100

‑n and Hypertension Edited by Philippe Meyer id Henri Schmitt New York 1979 John Wiley & Sons Inc ? pages. Price $42.50

inical and Laboratory Haematology (Journal) Edited by J England Oxford 1979 Blackwell Scientific Publications

Death and Psych atric Illness By Martin H Wend M.D Jamaica, N Y., 1979 Spectrum Publications Inc 9 pages. Price $20 00

›vascular Function Principles and Applications By L. Abel M D., Ph D and Ernest P McCutcheon ID Boston 1979 Little Brown & Company 4_1 pages ‑e $35 00

Advances in Experimental Medicine and B ology Dynam cs of Arterial Flow Vol 115 Edited by S Wolf and N T Werthessen New York and London 1979 Plenum Press 4‑2 pages Price $47 50

Enzymes in Cardiology Diagnosis and Research Edited by D J Hearse and J DeLeiris New York 1979 John Wiley & Sons Inc 5‑6 pages Price $70 00

Ischemic Heart Disease By I K. Shkhvatsabaya St Louis 1979 The C V Mosby Company 413 pa es Price $37 50

Controll ng the Smoking Ep demic World Health Organization Expert Committee on Smoking Control (Technical Report Series) Geneva 1979 World Health Organization 8 pages Price 9 Swiss francs.

Essential Hypertension Edited by Richard H Thurm M D Chicago 19‑9 Year Book Medical Publishers Inc., 41 pages

Michael M Laks
John H Laragh
Lawrence J Laslett
Kenneth C Lasseter
Ralph Lazzara
Garrett Lee
Louis Lemberg
Arthur Leon
Michael Lesch
Herbert Levine
Robert I Levy
Howard P Lewis
Richard P Lewis
Anthony J Libanoff
Joseph Lindsay Jr
Bernard Lipman
Henry S Loeb
Merle Loken
Floyd D Loop
J Martinez Lopez
Reginald I Low
David T Lowenthal
Bernard Lown
Daniel S Lukas
Harold A Lyons
Oscar Magidson
William J Mandel
George V Mann
John A Mantle
R Davis Manning Jr
Barry J Maron
H Marriott
Richard H Martin
B L Martz
Jay Mason
Barry M Massie
H Page Mauck Jr
Ben D McCallister
Robert McDonald
Dwight C McGoon
Paul McHenry
Dan G McNamara
Jawahar Mehta
Lawrence E Meltzer
Milton Mendlowitz
Arthur J Merrill
Richard A Meyer
Richard R Miller
David Mirvis
Jere H Mitchell
William J Mogabgab
E. Neil Moore
Joel Morganroth
Hiltrud S Mueller
Joseph P Murgo
Gerald W Murphy
Robert J Myerburg
Onkar S Narula
William P Nelson
R. Joe Noble
Jacqueline A Noonan
James J Nora
Jan Nyboer
Philip B Oliva
Lionel H Opie
Edward S Orgain
Robert A O Rourke
Hyman W Paley
Roger F Palmer
George A Pankey
Alfred F Parisi
William W Parmley
Oglesby Paul
Morton Lee Pearce
Alan S Pearlman
Oscar Pereda
Joseph K Perloff
Kirk L Peterson
Brendan Phibbs
Hubert V Pipberger
Bertram Pitt
Gerald M Pohost
Richard L. Popp
Leon Pordy
J M Pouget
William J Powell Jr
William L Proudfit
Raymond D Pruitt
Ray Pryor
Eric N Prystowsky
Charles E Rackley
Shahbudin H Rahimtoola
Robert A Ratshin
Pratap Reddy
Thomas A Riemenschneider
James L. Ritchie
Robert Roberts
William C Roberts
William J Rogers
Kenneth M Rosen
Michael R Rosen
John Ross Jr
Abraham M Rudolph
Richard O Russell Jr
David A Rytand
David J Sahn
Philip Samet
Miguel Sanmarco
Don R Santschi
Dante C Scarpelli
Melvin Scheinman
Leonard Scherlis
Nelson B Schiller
Robert C Schlant
Sidney Schnur
Fred W Schoonmaker
John S Schroeder
David C Schwartz
Ronald H Selvester
Arthur Selzer
Ralph Shabetai
Pravin M Shah
William Shapiro
James Shaver
L. Thomas Sheffield
Sol Sherry
Earl K Shirey
Bramah Singh
Harold Smulyan
Harbhajan S Sodhi
Louis Soloff
Walter Sommerville
Edmund H. Sonnenblick
Madison S Spach
James F Spann, Jr
David H. Spodick
Daniel J Stechschulte
Karl Stoedefalke
D E Strandness, Jr
Harold C Strauss
Borys Surawicz
H J C Swan
Abdul J Tajik
Robert C Tarazi
James H Thomsen
Bernard Towers
Naip Tuna
Elbert P Tuttle Jr
Richard Van Praagh
Philip Varriale
Stephen Vatner
Zakauddin Vera
Paul Vignola
Galen S Wagner
Albert L. Waldo
Paul Walinsky
J David Wallin
Paul F Walter
Myron L. Weisfeldt
Harvey J Weiss
Arthur E. Weyman
Leslie Wiener
James T Willerson
David O Williams
John F Williams, Jr
Roberta Williams
Roger A. Winkle
Stephen M Wittenberg
Taylor M. Wray
K E Wright
Barry L. Zaret
Robert F Zelis
Henry Zimmerman
Douglas P Zipes

American Heart Journal

December 1980 Volume 100 Number 6 part 1

Acknowledgment to reviewers

The Editors wish to express their thanks and appreciation to the members of the Editorial Board and to the following who have aided in the review of manuscripts during the past year

Abdul Abbasi
Francois Aboud
J A Abildskov
Herbert Abrams
Robert F Ackerman
Robert J Adolph
Masood Akhtar
Philip O Alderson
James K Alexander
Sidney Alexander
Hugh D Allen
Joseph A Alpert
Kurt Amplatz
Ezra A Amsterdam
Gary J Anderson
E T Angelakos
Mark L Armstrong
Wilbert A Aronow
William Aronow
Morton Arnsdorf
W Gerald Austen
Domingo M Aviado Jr
Najam A Awan
Daniel Azarnoff
John C Bailey
Donald W Baker
Robert W Barnes
Serge S Barold
Michael Barrett
Thomas Bassler
Lofty Basta
Benjamin Befeler
Alberto Benchimol
Woodroe Benson
Arthur Berenbaum
Gerald Berenson
Harvey Berger
Robert L Berger
Daniel S Berman
Robert M Berne
Sol Bernstein
J Thomas Bigger
Michael Bilitch
Peter F Binnion
Henry W Blackburn
Selvyn B Bleifer
John P Boineau
William J Bommer
Lawrence I Bonchek
Robert Bond
Jeffrey S Borer
Nemat O Borhani
Elias H Botvinick
Robert Boucek
H Boudoulas
Nancy Boyer
J David Bristow
Robert A Bruce
C E Buckley III
L Maximilian Buja
Bernadine H Bulkley
Benjamin Burrows
C A Caceres
Edgar Caldwell
David S Cannom
Paul Cannon
Antonio Caracta
Dennis J Carlson
Albert A Carr
David B Case
Augustin Castellanos Jr
Robert F Castle
Kanu Chatterjee
Melvin D Cheitlin
Shu Chien
John S Child
Rory Childers
Te Chuan Chou
Stephen D Clements Jr
Jay D Coffman
Lawrence S Cohen
Jay N Cohn
Keith E Cohn
Lawrence H Cohn
Peter F Cohn
James S Cole
H Neal Coleman III
John J Collins Jr
Robert D Conn
C Richard Conti
Gene Conway
Betty C Corya
James Covell
Ernest Craige
Richard S Crampton
Michael E Crawford
I Sylvia Crawley
J Michael Criley
James E Crockett
James E Dalen
Anthony N Damato
Antonio C DeLeon Jr
Anthony N DeMaria
R W DeSanctis
Ramesh C Dhingra
James C Dillon
Harold T Dodge
James E Doherty III
Philip Dow
Gordon E Dower
Marvin I Dunn
Harriet P Dustan
Barry Dzindzio
Paul A Ebert
E E Eddleman Jr
Jesse E Edwards
L D Edwards
Robert S Eliot
Myrvin H Ellestad
Mary Allen Engle
Michael Epstein
Stephen E Epstein
Doris J W Escher
Edward H Estes, Jr
Gordon A Ewy
David P Faxon
Harvey Feigenbaum
Alvan R Feinstein
Joel M Felner
Gerald F Fletcher
Nancy C Flowers
James M Foerster
Alan D Forker
James S Forrester
Noble O Fowler
Harry A Fozzard
Joseph A Franciosa
Walter Freyberger
Gottlieb C Friesinger
Victor F Froelicher
Edward D Frohlich
Seymour Furman
Thomas E Gaffney
John J Gallagher
W Horsley Gantt
William Ganz
J Genest
Ray W Gifford Jr
Charles Gilbert
Paul C Gillette
Thomas R Glatter
Herman K Gold
Eliot Goldstein
Robert E Goldstein
Stanley S Goodman
John F Goodwin
Thomas Gorsuch
Antonio M Gotto Jr
Alexander Gottschalk
K Lance Gould
Thomas B Graboys
Thomas P Graham Jr
Raymond Gramiak
David G Greene
Gabriel Gregoratos
Joseph Greenfield Jr
Kalman Greenspan
Robert L Grissom
William Grossman
Rolf M Gunnar
Warren G Guntheroth
Arthur D Hagan
Robert Hall
Victor E Hall
Robert I Hamby
E William Hancock
A Sidney Harris
Fred J Harris
W Proctor Harvey
Donald D Heistad
Milton R Hejtmancik
Richard H Helfant
Robert H Heinle
Walter L Henry
Michael Heymann
Roger B Hickler
L E Hinkle Jr
Eugene Z Hirsch
Irwin Hoffman
Julien I E Hoffman
Leo G Horan
Maysie J Hughes
Herbert N Hultgren
J O Neal Humphries
J Willis Hurst
Grover M Hutchins
Thomas N James
Carl E Jones
Mark E Josephson
James A Joye
William B Kannel
Norman Kaplan
Samuel Kaplan
Joel S Karliner
John A Kastor
Harold L Kennedy
Kenneth M Kent
Richard E Kerber
Philip Kimbel
Spencer B King III
John W Kirklin
Joseph A Kisslo
Richard M Klein
Frank E Kloster
Nicholas T Kouchoukos
Louis Kuller

plete medical inventory including cardiac evaluation prior to pregnancy To start a pregnancy and then learn later that a serious illness such as cardiac disease exists only introduces problems which could have been prevented A satisfactory medical inventory can be obtained by a general or family physician or internist A cardiologist may be consulted if necessary Since any qualified cardiologist must be an equally qualified internist he can study the patient initially in close cooperation with the physician who is responsible for the obstetrics Should illness be found which would increase the risk of pregnancy then the findings should be clearly explained and discussed with the patient and her husband These discussions should involve the family physician and cardiologist if the cardiologist has been engaged in consideration Most congenital heart disease advanced valvular heart disease and large hearts (especially in the presence of congestive heart failure) are contraindications for pregnancy The patient should be the only one who can decide to have a pregnancy in spite of risks She should then be advised that close clinical surveillance and cardiac management will be necessary throughout the pregnancy and especially near and at the time of delivery

Patients should also be reminded that having a baby is relatively simple whereas rearing one is strenuous ever demanding and a never ending problem even for normal people Patients with relatively mild heart disease at the time of pregnancy and delivery may have no serious difficulties during the pregnancy and during delivery but over the succeeding years the cardiac disease is most likely to worsen Then the mother would suffer from the stresses of rearing a baby and may become incapacitated or die when the child needs a mother most The much needed mother would leave a young offspring to suffer from the many difficulties of the world and possibly become a teenage problem or a social and economic delinquent Planning and considerations for pregnancy must not only take into consideration the immediate period of pregnancy but the years in the future as well These and other obvious considerations must be foremost in the physician s mind at all times The social economic and family prognoses are the responsibilities of the family physician—the counselor of the patient her husband and her family—as well as of all physicians concerned

If a patient already has young children (three others for example) it must be judiciously determined whether or not she should undertake the risk of another pregnancy possibly to be crippled for life or to die and leave behind a new baby and three young siblings and a father Imagine what could happen to these five people left behind without the mother! Remember the whole family all people must be considered

The physician should discuss with the family certainly with the married couple alone or with whomever else they wish the many implications risks advantages and potential problems that may ensue if pregnancy were to develop in the presence of the cardiac disease state To merely recommend pregnancy and to assist the woman through pregnancy only for the mother to succumb a few years later is not a praiseworthy accomplishment

Once pregnant the patient regardless of her state of health certainly should consult her family doctor immediately to evaluate her state of health and cardiac state in order to determine whether or not pregnancy should be allowed to continue Also remember that some of the drugs required for the care of her heart disease may produce a congenital anomaly in the fetus A cardiologist may be consulted if necessary when a patient is pregnant and has heart disease These health evaluations should be made within the first 3 months of pregnancy and preferably within the first 6 weeks in the event abortion is to be seriously considered When an abortion is considered and is carefully and thoroughly discussed by the family physician and obstetrician first and only after the medical aspects of the problems are thoroughly understood as mentioned for pregnancy evaluation then the patient and her husband should be consulted The cardiac disease state should be properly evaluated and the decisions made as to whether or not pregnancy can or is to continue in spite of the cardiac disease A competent cardiologist may need to be engaged to assist in the evaluation of the risks and in the management of the cardiac disease and to learn the problems to be expected during pregnancy and delivery and even after delivery When advanced heart disease is present the patient should be admitted to the hospital for the last 3 to 4 weeks of pregnancy when necessary to manage the heart disease and the pregnancy The obstetrician decides if when and how to induce labor when induction is necessary

When pregnant patients present themselves

To the readers of the American Heart Journal

Since 1959 I have had the pleasure of serving as Editor of the AMERICAN HEART JOURNAL During this time the Journal has flourished and enjoyed a wide readership which is a credit to the many contributors and to the Editorial Board the many reviewers and The C V Mosby Company all of whom provided excellent assistance to me and to the AMERICAN HEART JOURNAL. I wish to express my thanks to all who have helped make the Journal a success This assistance has come in a large part from readers from all over the world The main objective of the Journal has been to help its readers especially those dedicated to the practice of bedside and office medicine and cardiology I hope the AMERICAN HEART JOURNAL has served this purpose effectively

As I turn the Journal over to a new Editor I wish him and the AMERICAN HEART JOURNAL continued success

George E Burch M D

Editorials

Certain principles in the management of heart disease and pregnancy

G E Burch M D
New Orleans La

In addition to health problems due to pregnancy itself a pregnant woman can develop any disease that a non pregnant woman can develop However pregnancy normally imposes changes in the cardiovascular system which usually aggravate any associated illness of the cardiovascular system and which produce extra difficulty with the outcome of the pregnancy The normal and abnormal changes associated with pregnancy are particularly prominent in the presence of heart disease Heart disease is a serious illness in itself without the imposition of pregnancy to increase this seriousness Furthermore there are some cardiac states associated with pregnancy which actually are of little importance but which often concern the patient and her family and her obstetrician Examples include premature heart beats When such rhythm disturbances are present during pregnancy the concern about them becomes even greater than usual Therefore there are certain general clinical medical principles which should be considered in pregnancy Some of these principles are discussed below

Any woman contemplating or planning a pregnancy should be examined carefully for a com

From the Department of Medicine Tulane University School of Medicine and the Charity Hospital of Louisiana New Orleans

Received for publication Feb 4 1980

Reprint requests Dr George E Burch, Dept of Medicine Tulane University School of Medicine 1430 Tulane A N w Orleans, La 7011.

000? 8 03/80/1?0775 + 03$00 30/0 © 1980 The C V Mosby Co

Thermal illness in fun running

John R Sutton MB BS FRCP(C)
Oded Bar Or, M D
Hamilton Ontario Canada

Almost weekly in the medical press, we read of a new complication associated with jogging—bruises blisters sprains tears penile frostbite, excoriated nipples, osteoarthritis myocardial infarction heat stroke asthma hypoglycemia amenorrhea nephropathy etc One could be forgiven for thinking that a pair of running shoes is an invitation to self destruction[1]

These problems multiply when the jogger is encouraged to join his compatriots for a fun run for the addition of the competitive aspect may be an ingredient responsible for the most serious of the fun runner s problems thermal injury Heat stroke is the most serious of the thermal injuries for not only can it kill but the potential number of those severely afflicted is alarmingly large It appears that fun running is still in its ascendancy and now with more than 30 million joggers on the North American continent the number of heat casualties resulting from fun runs could reach epidemic proportions

There are many reports of serious heat injuries heat exhaustion and heat stroke during fun runs in Australia Canada[5,6] New Zealand[7,8] and the United States[9] In the United States experience probably the Peachtree Road Race in Atlanta has produced the greatest number of heat casualties One usually associates heat injury with hot humid environments however, this is not necessarily so in fun runs as the Sydney 'City to Surf' experience demonstrates Heat stroke in runners with rectal temperatures as high as 43° C have been recorded when the ambient temperature was as low as 10° C or a correc effective temperature (which takes i to a count humidity and wind) of only 5° C

What is the predictable setting in which he injury will occur? Obviously the combination environmental factors and the predisposed in vidual will be the right mix for serious he injuries to occur From the City to Surf" expe ence, in the four years from 1976 to 1979 inclusi no case of heat exhaustion or heat stroke h occurred in a registered athlete who has de oped the art of listening to signals of fatigue a stress from the body [11] It is also clear that t risk of sustained heat related injuries is not t same for all runners There are large individ differences in heat tolerance and therefore p disposition to heat injury Following are some the factors known to characterize an indiv d who is at greater risk

1 **Insufficient acclimatization** For an unac matized subject running in a hot environm will produce an excessively high physiolog strain—higher core and skin temperatures a higher heart rate and running capacity w decline markedly This can occur classically wh an athlete is transferred from a cool to a h environment if training is done in the cooler pa of the day but competition is conducted in of the day or if there is an unexpec heat of the day or if there is an unexpec climatic change It takes about 5 to 10 run sessions in the new climate before these str indices return to previous levels and only t will the runner perform at his previous level the transition period athletes should reduce b the intensity and duration of training runs It been clearly shown that a disregard for th precautions will lead to unduly high heat stor and predisposition to heat illness including h stroke [13,14]

From the Departments of Medicine and Paediatrics McMaster University Hamilton Ontario Canada

Received for publication March 18 1980

Reprint requests Dr John R Sutton Room 3U26 McMaster University Medical Centre Box 2000 Station A Hamilton Ontario Canada L8N 3Z5

0002 8703/80/1 0778 + 04$00 40/0 © 1980 The C V Mosby

in pregnancy with heart disease the physi and obstetrician and the anesthesiologist consult in regard to managing the future of the pregnancy Such problems must be dividualized since no two situations are precise ly the same Close cooperation of all physicians is essary to render adequate service to the preg patient

The methods of managing a patient who is and suffering from heart disease will upon many factors It is impossible to ndicate the management in detail or even to list all of these factors The best cardiologist and the best obstetrician are necessary for the most severe uations The technics of delivery etc must be left to the obstetrician and the anesthesia to the anesthesiologist after the clinical situation has been thoroughly studied and discussed by these physicians The general physician and/or cardiol ogist must begin their management of the heart disease as early as possible prior to delivery It is a mistake to wait to start cardiac therapy or to begin anticipating problems until after they have occurred Proper early predelivery management with proper planning prior to delivery for the time of delivery with anticipation of problems can e for a successful and happy outcome Management continues during the puerperal peri od Decisions do not end with a successful deliv ery Continued management of the cardiac dis ease and considerations of the prevention of future pregnancies is mandatory

With greater emphasis on prepregnancy exami nations and with routine premarital and prepreg nancy examinations with thorough discussions the problems related to heart disease and preg nancy could be reduced to a minimum and deaths of mothers due to heart disease and pregnancy could be practically eliminated The time to learn about the safety or hazards of pregnancy is *prior* to pregnancy This is true not only for heart disease but for all other disease states as well Young girls and women who have not had a thorough medical evaluation including a cardiac examination should have one prior to engaging in sexual activity with possible resultant pregnancy Such an evaluation certainly is indicated immedi ately after detecting pregnancy The decision to follow up these studies must be individualized

When patients with heart disease are not seen until the last trimester of pregnancy or just prior to the onset of labor the family physician and/or cardiologist must work closely with the obstetri cian and anesthesiologist in management with all necessary preparations procedures and equip ment being made available during delivery The patient with heart disease regardless of how mild the problem should be continually managed by the family or primary doctor Congestive heart failure offers the greatest difficulty This is espe cially true when acute congestive heart failure develops during delivery Shock or serious cardiac arrhythmia may further worsen the clinical prob lems All of these complicated cases are most difficult to manage even by experts with consid erable experience

loads than when exercising in neutral environments[45] Surprising to some may be the fact that death from hypothermia may occur in fun runs when the exhausted lightly clad athlete runs in a cold windy environment[6]

It would therefore seem that jogging may not be safe at any time of the year But there is another side isn t there? Far from trying to stifle the present worship of physical activity, which shows no signs of being just a passing fad we too are of the faith and have also suffered some of the wounds albeit minor, of the jogging martyrdom However we do want to add a note of caution when we encourage people to be active and participate because if they are injudicious they may pay a heavy price Above all we must keep the fun in fun runs!

REFERENCES

1 Sutton J Coleman M K Millar A P Lazarus, L and Russo P The medical problems of mass participation in athletic competition The City to Surf race Med J Aust 2 127 1972

2 Richards R Richards D Schofield P J Ross V and Sutton J R Reducing the hazards in Sydney s The Sun City to Surf runs 1971 1979 Med J Aust 2 453 1979

3 Richards D Richards R Schofield P J Ross V and Sutton J R Management of heat exhaustion in Sydney s The Sun City to Surf fun runners Med J Aust 2 457 1979

4 Sutton J R 43 C in fun runners' Med J Aust 2 463 1979

5 Hughson R L Green H J Houston M E. Thomson J A MacLean D R and Sutton J R Heat injuries in Canadian mass participation runs Can Med Assoc J 122 1141 1980

6 Hart L E Egier B P Shimizu A G Tandan P J and Sutton J R Exertional heat stroke The runner s nemesis Can Med Assoc J 122 1144 1980

7 Nicholson R N and Somerville K W Heatstroke in a run for fun Br Med J 1 1525 1976

8 Roydhouse N Karn H and Johnson L Round the Bays 17.92 km fun run for 25 000 entrants, N Z. J Sports Med 6 4 1978

9 Hanson P G and Zimmerman S W Exertional heatstroke in novice runners J A M A 242 154 1979

10 Noble H B and Bachman D Medical aspects of distance race planning Physician Sportsmed 7 78 1979

11 England A C (Personal communication 1979)

12 Hughson R L and Sutton J R Heat stroke in a run for fun Br Med J 2 1158 1978

13 Knochel J P Environmental heat illness an eclectic review Arch Intern Med 133 841 1974

14 Shibolet S Lancaster M L and Danon Y Heat stroke a review Aviat Space Environ Med 47 280 1976

15 Drinkwater B L Kuppart I C Denton J E., and Horvath S M Heat tolerance of female distance runners Ann N Y Acad Sci 301 777 1977

16 Gisolfi C V and Cohen J Relationships among training heat acclimation and heat tolerance in men and women the controversy revisited Med. Sci. Sports 11 56 1979

17 Piwonka R W., Robinson S Gay V L., and Marsh R S Preacclimatization of men to heat by training J Appl Physiol 20 379 1965

18 Shvartz E., Shapiro Y., Magazanik A Meroz, A Birnfeld H Mechtinger A and Shibolet, S Heat acclimation physical fitness and responses to exercise in temperate and hot environments J Appl Physiol Respirat Environ Exercise Physiol. 43 6 8 19

19 Pandolf K B Burse R L. and Goldman R F Role of physical fitness in heat acclimatization decay and reinduction Ergonomics 20 399 1977

20 Pugh L. G C E Corbett J L. and Johnson, R H Rectal temperatures weight losses and sweat rates in marathon running J Apply Physiol. 23 347 1967

21 Wyndham C H and Strydom N B The danger of inadequate water intake during marathon running, S Afr Med J 43 893 1969

22 Costill D L Coté R Miller E Miller T and Wynder S Water and electrolyte replacement during repeated days of work in the heat Aviat Space Environ Med 46 795 1970

23 Greenleaf J E. and Castle B L. Exercise temperature regulation in man during hypohydration and hyperhydration J Appl. Physiol. 30 847 1971

24 Bar Or O Dotan R Inbar O Rotshtein A, and Zonder H Voluntary hypohydration in 10 to 12 year old boys J Appl. Physiol Respirat Environ Exercise Physiol 48 104 1980

25 Bar Or O Harris, D Bergstein V and Buskirk E R Progressive hypohydration in subjects who vary in adiposity Isr J Med Sci 12 800 1976

26 Ellis F P Exton Smith A. N Foster K G and Weiner J S Eccrine sweating and mortality during heat waves in very young and very old persons, Isr J Med Sci. 12 815 1976

27 Drinkwater B L. and Horvath S M Heat tolerance and aging Med Sci. Sports 11 49 1979

28 Van Beaumont W Thermoregulation in desert heat with respect to age Physiologist 8 294 1965

29 Wagner J A Robinson S Tzankoff S P and Marino R. P Heat tolerance and acclimatization to work in the heat in relation to age J Appl Physiol. 33 616 1972

30 Bar Or O Climate and the exercising child—a review Int J Sports Med 1 53 1980

31 Inbar O Acclimatization to dry and hot environment in young adults and in children 8 10 years old Ed.D. Dissertation Columbia University 1978

32 Haymes E M McCormick R J and Buskirk E R Heat tolerance of exercising lean and obese boys, J Appl Physiol 39 457 1975

33 Bar Or O Lundegren H M and Buskirk, E R Heat tolerance of exercising lean and obese women J Appl Physiol. 26 403 1969

34 Barcenas C., Hoeffler H P., and Lie J T Obesity football dog days and siriasis A deadly combination Am Heart J 92 237 1976

35 Fox E L., Mathews D K Kaufman W S and Bowers R W Effects of football equipment on thermal balance and energy cost during exercise Res Q Am. Assoc Health Phys Ed 37 332 1966

36 Malamud N Haymaker W., and Custer R. P Heat stroke A clinicopathologic study of 125 fatal cases, Mil Surg 99 397 1946

37 Schrier R W Henderson S H Tisher C C and Tannen R L. Nephropathy associated with heat stress and exercise Ann. Intern Med 67 356 1967

38 Shapiro Y Magazanik A Udassin R Ben Baruch, G

2 Lack of conditioning Conditioning in a cool climate can only partially substitute for exercise in the heat as a means for acclimatization Still the less conditioned female[15, 16] or male[1, 1] runner does seem to be less heat tolerant Less conditioned individuals also take longer to acclimatize to heat [19] Inexperienced runners may sustain heat stroke during races not necessarily due to low fitness level but rather because they select a running speed which is too fast for their ability [9]

3 Dehydration Progressive dehydration commonly occurs during long distance running even when fluids are supplied ad libitum Although the runner can perform well while being dehydrated, extreme fluid losses predispose one to heat stroke and acute renal failure Of special importance is the hydration level prior to a run Those who start exercising while dehydrated reach a higher core temperature than they would when fully hydrated prior to the exercise [3] Thus if a runner neglects to be fully hydrated before a prolonged run the risk of inadequate heat dissipation is magnified When progressively dehydrating during prolonged exercise children and obese individuals [5] have a greater rise in core temperature than do lean young adults

4 Age extremes Both young children and elderly people are more susceptible than young adults to climatic heat waves [6] During prolonged exercise in the heat children were found to have shorter tolerance time than had young adults [13, 27, 30] *This difference is especially evident* in very hot climates (dry bulb exceeding 40 C) and is attributable to greater surface area/mass ratio lower sweating rate greater metabolic heat production and a less efficient convection of heat from core to skin in the child Young adolescents and children[31] can acclimatize to heat However children need more time than adults to reach sufficient acclimatization [3] Possible causes for low heat tolerance among the exercising elderly are a lesser sweat production and a lower aerobic capacity [27]

5 Obesity Obese teenagers and adults are less heat tolerant than are lean individuals The clinical relevance is that exercising overweight and obese people are at greater risk for heat illness including nephropathy and fatal heat stroke [34, 37]

6 Prior heat stroke What is the risk for a runner with a history of heat stroke to have a relapse during subsequent running? Young adults who had sustained heat stroke during a prolonged march in hot weather were given 2 to 5 years later an exercise test in a heated climatic chamber None of them managed to complete the task which was successfully completed by healthy controls [6] The reasons for incompletion were exhaustion or excessively high core temperature and heart rate Deficient thermoregulatory capacity in people who had a history of heat stroke was also described by Robinson and coworkers

An important question is whether such people have inherent deficiencies or whether their thermoregulatory capacity became irreversibly affected *during* the heat stroke episode This question cannot be answered by the above retrospective studies At any rate runners with a previous history of heat stroke are at a higher risk of recurrence and should be advised to avoid intense running in hot weather

Management

Much ha been written about the management of heat injuries and obviously prevention is the key particularly when one considers the large number of predisposed individuals in fun runs These findings have been adequately reviewed elsewhere [1, 4, 4] In general the recommendations have fallen into three categories (1) those related to *race organization*—i e timing of the race during the day and time of year possible cancellation of the race if heat stress indices reach extreme levels provision of adequate fluids (2) *competitor education*—information regarding training heat acclimatization awareness of potential problems and likely premonitory symptoms and (3) *medical management and organization* and provision of first aid stations and on site emergency treatment facilities for the rapid cooling of patients *

We have concentrated on heat injury in our coverage of the thermal problems related to fun runs as these cases are obviously numerically the most important However problems from cold or dry air arise in fun runners particularly those who may develop exercise induced asthma [3, 4] and those with ischemic heart disease who will develop angina on a cold day at lower exercise

N B S ce the inst t ti n of these rapid cooling f cil t es during the City to-Surf™ race there ha e been no serious sequel e f h t stroke in almost 100 000 competit rs

Clinical communications

Severity of coronary artery disease in patients with diabetes mellitus Angiographic study of 34 diabetic and 120 nondiabetic patients*

Carlo Vigorito M D
Sandro Betocchi M D
Giulio Bonzani M D
Pietro Giudice M D
Domenico Miceli M D
Federico Piscione M D
Mario Condorelli M D
Naples Italy

Although the higher incidence of mortality and morbidity for cardiovascular events in patients with diabetes mellitus (DM) compared with nondiabetic patients has evidentiated the role of DM as an independent risk factor for cardiovascular disease controversies still exist about the severity of coronary artery disease (CAD) in diabetic (D) compared to nondiabetic (ND) patients While some studies have shown an equal incidence of CAD others have reported a higher grade of severity of CAD in D patients compared to ND patients

Such controversies led us to re examine our data on 34 diabetic patients who had undergone selective coronary arteriography in the last 2 years in our institution and who were found to have significant CAD and to compare their clinical hemodynamic and angiographic findings with those of a control group of 120 nondiabetic patients with CAD studied consecutively in the same period of time

Patient population

Of the 34 patients with DM 30 were males and four were females with ages ranging from 39 to 68 years (mean 56 years) Patients were consider[...] as diabetic if they were on medical treatment f[...] DM or if they had two abnormal fasting blo[...] sugar values The majority of them (30 of 34) we[...] on oral hypoglycemic agents The group of N[...] patients was composed of 120 patients, 110 mal[...] and 10 females 37 to 67 years of age (mean [...] years)

Incidence of other coronary risk factors [...] similar in the two groups (Fig 1) Smoking [...] indulged in by 26 diabetic patients (76%) a[nd] [...] 89 nondiabetic subjects (74%), systemic hyp[er]tension was present in nine diabetic patie[nts] [...] (26%) and in 28 nondiabetic subjects (23[%]) Hyperlipidemia was found in 11 diabetic patie[nts] (32%) and in 24 nondiabetic subjects (20%) Th[ere] was a family history of CAD in eight diabe[tic] patients (24%) and in 30 nondiabetic subje[cts] (25%)

Fig 2 shows the clinical findings in the t[wo] groups Of 34 patients with DM 21 (64%) wer[e in] functional Class I to II and 12 (36%) were [in] functional Class III to IV of NYHA classificati[on] while of 120 nondiabetic subjects 80 (67%) wer[e in] Class I to II and 40 (33%) were in Class III to [IV] Stable angina was the clinical presentation [in] [...] diabetics (38%) and in 32 nondiabetics (27%) [...] diabetic patients (56%) and 61 nondiabetic [sub]jects (51%) presented with unstable ang[ina] defined as one of the following progressive an[gina] on effort angina at rest or intermediate [...] drome first onset angina Other prese[nting] symptoms (atypical angina dyspnea on exer[tion] [...]

From the Istituto di Patologia Medica Second Faculty of Medicine and Surgery University of Naples Naples, Italy

Received for publication N[...] 19[...]

Accepted for publication M[...] 198[...]

Reprint requests Carlo Vigorito M D Via G Vigorito 6 84100 Salerno Italy

*Preliminary data from this paper were presented as an abstract at the XL Italian Congress of Cardiology Bari, Italy June 1979

[...] © 1980 The C V Mosb[y] [...]

Shvartz E and Shoenfeld Y Heat tolerance in former heat stroke patients Ann Intern Med 90 913 1979
39 Robinson S Wiley S L Boudurant L G and Mamlin S Jr Temperature regulation of men following heatstroke Isr J Med Sci 12 786 1976
40 American College of Sports Medicine Position Statement Prevention of heat injuries during distance running Med Sci Sports 7 vii 1975
41 Sutton J R and Harrison H C Health hazards in community jogs and fun runs Med J Aust 1 193 1977
42 Sutton J R Hyperthermia in fun runs Medisport (In press)
43 Strauss R H McFadden E R Ingram R H and Yaeger J J Enhancement of exercise induced asthma by cold air N Engl J Med 297 743 1977
44 Bar Or O Neuman I and Dotan R Effects of dry and humid climate on exercise induced asthma in children and preadolescents J Allergy Clin Immunol 60 163 1977
45 Lassvik C and Areskog N H Effects of various environmental temperatures on effort angina Ups J Med Sci 84 173 1979
46 Sutton J Community jogging vs arduous racing N Engl J Med 286 951 1972

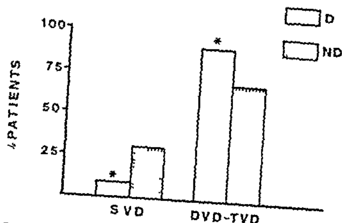


Fig 3 Incidence of multivessel disease *(DVD TVD)* and single vessel disease *(SVD)* in 34 diabetic *(D)* and 120 nondiabetic *(ND)* patients $p < 0.025$ D vs ND

Table I Hemodynamic data in 34 diabetic (D) and in 127 nondiabetic (ND) patients with coronary artery disease (*Mean ± SD*)

	LVEDP (mm Hg)	*CI (L/min/M)*	*LV dP/dT max (mm Hg/sec)*
D	18 6 ± 8	2 78 ± 8	1 660 ± 682
	NS	NS	NS
ND	19 5 ± 7	3 07 ± 9	1,855 ± 709

LVEDP left ventricular end-diastolic pressure CI cardiac index LV dP dT max maximal rate of rise of left ventricular systolic pressure

Table II Number of coronary stenoses in 34 diabetic (D) and 120 nondiabetic (ND) patients with coronary artery disease

	Patients (No)	*Stenosis (No)*	*Stenosis/ Patient*
D	34	82	2 41
			$p < 0.025$
ND	120	251	2 09

Results

Table I shows the principal hemodynamic data for both groups These results also include 7 diabetic patients in whom only hemodynamic data were obtained *without* angiographic studies Diabetics presented a lower cardiac index and left ventricular dP dT max but these differences were not statistically significant

The extent of CAD in diabetic and nondiabetic patients is shown in Fig 3 SVD was found in three of 34 diabetic (9%) and in 36 of 120 nondiabetic patients (30%) ($p = 0.025$) multivessel disease (DVD/TVD) was present in 31 of 34 diabetic (91%) and in 84 of 120 nondiabetic patients (70%) ($p < 0.025$) Number of coronary stenoses per patient was 2 47 in diabetic and 2 09 in nondiabetic patients ($p < 0.025$) (Table II)

Fig 4 shows the distribution of CAD on major coronary arteries Left anterior descending (LAD) was significantly involved in all 34 diabetic patients (100%) and was predominantly involved in nondiabetic patients (10? of 120 8?%) This difference between diabetics and nondiabetics had statistically significant results ($p < 0.005$) Right coronary artery (RCA) stenosis was found in 27 of 34 diabetic (79%) and in 8? of 120 nondiabetic patients (69%) Circumflex coronary artery (Cx) involvement was present in 21 of 34 diabetic (62%) and in 66 of 120 nondiabetic patients (55%) Incidence of complete coronary artery occlusions is also shown in Fig 4 At least one coronary occlusion was found in 15 of 34 diabetic (44%) and in 48 of 120 nondiabetic patients (40%) A total of 20 occlusions was found in the 15 diabetic patients (1 33 occlusions per patient) a total of 55 occlusions was found in the 48 nondiabetic patients (1 15 occlusions per patient) In both groups LAD and RCA were more frequently and almost equally occluded LAD occlusion was present in eight of 34 diabetic (23%) and in 25 of 120 nondiabetic patients (20%) Cx was occluded in four of 34 diabetic (12%) and in six of 120 nondiabetic patients (5%) Such differences were not statistically significant

Fig 5 shows the results of left ventriculography Eight of 32 diabetic (25%) and 56 of 115 nondiabetic patients (49%) presented with normal left ventriculography or only a localized asynergy ($p < 0.025$) No differences between diabetic and nondiabetic patients were found in the incidence of diffuse asynergy (14 of 32 diabetic 44% vs 43 of 115 nondiabetic patients 37%) Left ventricular *aneurysm* was present in 10 of 32 diabetic (31%) and in 16 of 115 nondiabetic patients (14% $p < 0.025$) In order to evaluate if the latter difference had to be attributed to *different severity or distribution of CAD* or to different development of collateral circulation we analyzed these factors in the 10 diabetic and in the 16 nondiabetic patients with LV aneurysm (Table III) No significant differences resulted in severity of CAD incidence of occlusion of the coronary artery supplying the aneurysmatic seg

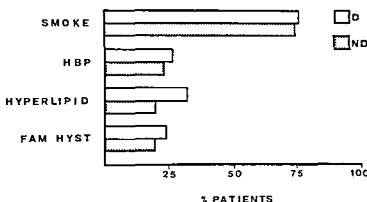


Fig 1 Incidence of risk factors for coronary artery disease in 34 diabetic *(D)* and 120 nondiabetic *(ND)* patients.

ere found in two diabetic patients (6%) and in 27 ondiabetic subjects (22%) Ischemic changes on e electrocardiogram were present in 14 diabetic atients (41%) and in 65 nondiabetic subjects 4%) A history of myocardial infarction (MI) as present in 20 diabetics (59%) and in 68 ondiabetics (57%) Cardiomegaly on chest x ray as found in 18 diabetic patients (52%) and in 50 ondiabetic subjects (42%) Mean duration of mptoms was 49 2 months in diabetics and 40 8 onths in nondiabetics None of the above differ nces was statistically significant

In both groups the indication for cardiac cath terization and coronary arteriography was given ased on the presence of angina stable or unsta le nonresponding to intensive medical manage ent or on the presence of symptoms such as entricular arrhythmias or atypical chest pain hen it was important to exclude or confirm the inical suspicion of CAD or finally on the resence of otherwise unexplained symptoms of ft ventricular (LV) failure

Methods of study All patients underwent car iac catheterization left ventriculography and elective coronary arteriography with the Sones echnique[1] Pressures were recorded with Sta ham P23Db transducers on an OTE photograph c recorder Cardiac output was measured by the hermodilution technique[3] Left ventriculogra hy was obtained by injecting 45 c c of Urografin 76% in the left ventricle at 15 c c /sec speed with Viamonte Hobbs injector with the patient posi ioned in the right oblique and sometimes also in the left oblique projection Selective coronary arteriography was also performed in multiple projections Left ventriculography and coronary arteriography were recorded on Kodak film with

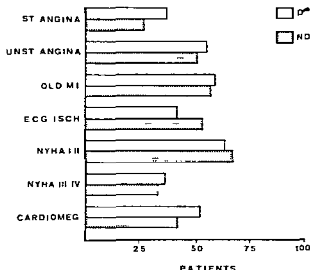


Fig 2 Clinical findings in 34 diabetic *(D)* and in 120 nondia betic *(ND)* patients See text for abbreviations.

the aid of a Fluoricon 300 General Electric image intensifier and a 105 mm spot camera at 6 to 8 frames/sec

The presence and severity of segmental LV wall contraction abnormalities were graded as fol lows (1) normal segmental contraction (2) local ized hypokinesia akinesia or diskinesia (3) diffuse hypokinesia akinesia or diskinesia and (4) LV aneurysm On the basis of coronary arteriog raphy patients were subdivided in single double and triple vessel disease (SVD DVD and TVD) according to the presence of significant narrow ings on one two or three major coronary arteries A stenosis equal or greater than 50% of luminal diameter was considered as significant

Statistical analysis was performed with the Student s t test and χ test

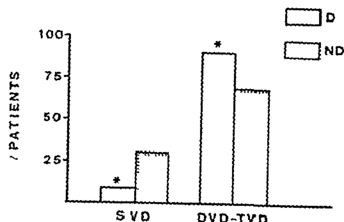


Fig 3 Incidence of multivessel disease *(DVD TVD)* and single vessel disease *(SVD)* in 34 diabetic *(D)* and 120 nondiabetic *(ND)* patients $p < 0.025$ D vs ND

Table I Hemodynamic data in 34 diabetic (D) and in 127 nondiabetic (ND) patients with coronary artery disease (Mean ± SD)

	LVEDP (mm Hg)	*CI (L/min/M)*	*LV dP/dT max (mm Hg/sec)*
D	18 6 ± 8	2 78 ± 8	1 660 ± 682
	NS	NS	NS
ND	19 5 ± 7	3 07 ± 9	1 855 ± 708

LVEDP left ventricular end-diastolic pressure CI cardiac index LV dP/dT max maximal rate of rise of left ventricular systolic pressure

Table II Number of coronary stenoses in 34 diabetic (D) and 120 nondiabetic (ND) patients with coronary artery disease

	Patients (No)	*Stenosis (No)*	*Stenosis/ Patient*
D	34	82	2 41
			p < 0 025
ND	120	251	2 09

Results

Table I shows the principal hemodynamic data for both groups These results also include 7 diabetic patients in whom only hemodynamic data were obtained without angiographic studies Diabetics presented a lower cardiac index and left ventricular dP/dT max but these differences were not statistically significant

The extent of CAD in diabetic and nondiabetic patients is shown in Fig 3 SVD was found in three of 34 diabetic (9%) and in 36 of 120 nondiabetic patients (30%) ($p = 0.025$) multivessel disease (DVD/TVD) was present in 31 of 34 diabetic (91%) and in 84 of 120 nondiabetic patients (70%) ($p < 0.025$) Number of coronary stenoses per patient was 2 47 in diabetic and 2 09 in nondiabetic patients ($p < 0.025$) (Table II)

Fig 4 shows the distribution of CAD on major coronary arteries Left anterior descending (LAD) was significantly involved in all 34 diabetic patients (100%) and was predominantly involved in nondiabetic patients (102 of 120 85%). This difference between diabetics and nondiabetics had statistically significant results ($p < 0.005$) Right coronary artery (RCA) stenosis was found in 27 of 34 diabetic (79%) and in 83 of 120 nondiabetic patients (69%) Circumflex coronary artery (Cx) involvement was present in 21 of 34 diabetic (62%) and in 66 of 120 nondiabetic patients (55%) Incidence of complete coronary artery occlusions is also shown in Fig 4 At least one coronary occlusion was found in 15 of 34 diabetic (44%) and in 48 of 120 nondiabetic patients (40%) A total of 20 occlusions was found in the 15 diabetic patients (1 33 occlusions per patient) a total of 55 occlusions was found in the 48 nondiabetic patients (1 15 occlusions per patient) In both groups LAD and RCA were more frequently and almost equally occluded LAD occlusion was present in eight of 34 diabetic (23%) and in 25 of 120 nondiabetic patients (20%) Cx was occluded in four of 34 diabetic (12%) and in six of 120 nondiabetic patients (5%). Such differences were not statistically significant

Fig 5 shows the results of left ventriculography Eight of 32 diabetic (25%) and 56 of 115 nondiabetic patients (49%) presented with normal left ventriculography or only a localized asynergy ($p < 0.025$) No differences between diabetic and nondiabetic patients were found in the incidence of diffuse asynergy (14 of 32 diabetic 44% vs 43 of 115 nondiabetic patients 37%) Left ventricular aneurysm was present in 10 of 32 diabetic (31%) and in 16 of 115 nondiabetic patients (14% $p < 0.025$) In order to evaluate if the latter difference had to be attributed to different severity or distribution of CAD or to different development of collateral circulation we analyzed these factors in the 10 diabetic and in the 16 nondiabetic patients with LV aneurysm (Table III) No significant differences resulted in severity of CAD incidence of occlusion of the coronary artery supplying the aneurysmatic set

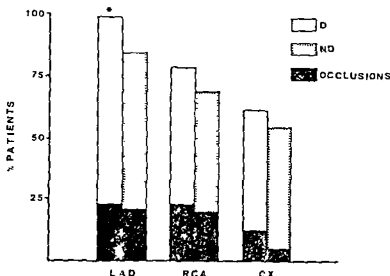


Fig 4 Frequency of significant stenoses and occlusions of major coronary arteries in 34 diabetic *(D)* and 120 nondiabetic *(ND)* patients $p < 0.005$ D vs ND

ment and extent of collateralization to the infarcted myocardial area

Discussion

Patients with and without diabetes mellitus showed similar incidence of CAD risk factors such as systemic hypertension smoking habits and family history of CAD Differences in age and incidence of hyperlipidemia were only minimal and were not statistically significant Although the presence of diabetes mellitus might influence the indication to cardiac catheterization and thus preselect patients with more severe CAD this was unlikely to be the case in our population Over the last two years we felt that the poor angiographic quality of coronary arteries in diabetic patients which rendered them not suitable for aortocoronary bypass grafts did not justify reserving coronary arteriography only in diabetic patients with more severe angina In fact although in our study diabetics showed a slightly larger incidence of angina compared to nondiabetic patients (94% vs 78%) the frequency of the more severe type of angina (unstable) was practically the same (56% vs 51%) and all other clinical parameters that we analyzed were comparable Thus we feel that diabetic and nondiabetic patients in our study can be considered as two matched groups with CAD only differing in the presence or absence of diabetes mellitus which by itself should explain the differences in the severity and distribution of CAD between the two groups

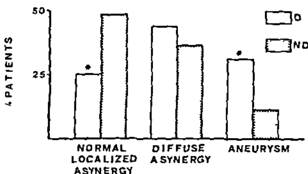


Fig 5 Findings at left ventriculography in 3? diabetic *(D)* and 115 nondiabetic *(ND)* patients $p < 0.025$ D vs ND

Other authors have compared the extent of CAD in diabetic and nondiabetic patients based upon angiographic[6, 8] or pathologic[4, 5, 9, 11, 16] data Recently Dortimer and associates[8] reporting coronary arteriographic findings in 37 diabetic and in 79 nondiabetic patients matched for age sex and CAD risk factors, have described in patients with diabetes mellitus a significantly higher number of diseased coronaries per patient and a higher although not significant incidence of TVD compared to nondiabetic patients Furthermore they found no differences in the distal distribution of CAD in the incidence of bypassable vessels distal to a significant stenosis and in the frequency of collaterals to occluded coronaries They did not comment though on differences in the degree of impairment of LV segmental contraction between the two groups In

Combined mexiletine and amiodarone treatment of refractory recurrent ventricular tachycardia

A Waleffe MD PhD
L Mary Rabine MD FACC
V Legrand MD
J Cl Demoulin MD
H E Kulbertus MD FACC
Liège Belgium

Refractory recurrent ventricular tachycardia represents a difficult therapeutic problem In most cases the rhythm disorder ultimately requires the administration of a multiple drug regimen Potentiation of the efficacy of one drug by the other is possible and satisfactory clinical results may be expected with lower doses than if each agent were given singly This might decrease the incidence of at least some of the side effects

The present paper is concerned with the results obtained in nine patients by using the association of a class I antiarrhythmic agent (mexiletine) with a class III agent (amiodarone)

Description of patients and methods

The study group consists of nine male patients ranging in age from 23 to 64 years (mean 53 4 years) and suffering from recurrent episodes of documented ventricular tachycardia The first three of these cases were very critically ill individuals who had spent 10 days or more in the intensive care unit with at least five episodes of ventricular tachycardia daily (Table I) In each instance several antiarrhythmic agents had been administered in classical dosage without any success It is to be noted that all three patients had received intravenous mexiletine at a dose of 1 500 mg per day This had reduced or suppressed the episodes of arrhythmia but serious gastrointestinal disorders (vomiting) had developed in all three and neurological side effects consisting of convulsions (type grand mal) had occurred in one (patient No 3) Reduction of the dose to 1000 mg per day had allowed the rhythm disorder to recur The remaining six cases (Table II) had a diagnosis of coronary artery disease (five patients) or congestive cardiomyopathy (one patient) They all had suffered repeated episodes of ventricular tachycardia which could not be prevented by the various drugs previously administered These patients were referred to the laboratory of clinical electrophysiology for determination of optimal pharmacological therapy After informed consent all cardioactive drugs were discontinued for at least 72 hours before the electrophysiologic investigation by programmed electrical stimulation of the heart was conducted The methods apparatus and definitions used have been previously described[1] The stimulation sequence which permitted the induction of ventricular tachycardia was characterized by using different atrial and ventricular pacing rates (up to ... /minute) and one to four ventricular premature depolarizations Once initiation of tachycardia was achieved by pacing the treatment by amiodarone and mexiletine was begun as indicated below To judge the efficacy of this drug regimen the patients were submitted to iterative electrophysiologic testing on days 5 and 7 after initiation of therapy On each occasion the complete program of atrial and ventricular stimulation was repeated

From the Division of Cardiology Institute of Medicine University of Liège Belgium

Received for publication Dec 26 1979
Accepted for publication March 6 1980

Reprint requests Henri E Kulbertus MD Division of Cardiology University of Liège Hopital de Bavière 66 Bvd de la Constitution B 4020 Liège Belgium

0002-8703/80/120788 + 06$00 60/0 © 1980 The C V Mosby Co

R Lipid and carbohydrate abnormalities in patients with angiographic documented coronary artery disease Am J Cardiol 24 178 1969

3. Kennel W B and McGee D L Diabetes and cardio vascular risk factors the Framingham study Circulation 59 8 1979
4. Vihert A M Zhdanov V S and Matova E E Atherosclerosis of the aorta and coronary vessels of the heart in cases of various diseases, Atheroscler Res 9 179 1969
5. Ledet T Histological and histochemical changes in the coronary arteries of old diabetic patients Diabetologia 4 268 1968
6. Verska J J and Walker W J Aorto coronary bypass in the diabetic patient Am J Cardiol 35 774 1975
7. Pell S and D Alonzo C A Factors associated with long term survival of diabetics J.A.M.A 214 1833 1970
8. Dortimer A C Shenoy P N Shiroff R A Leamann D M Babb J D Liedtke A J and Zeli R Diffuse coronary artery disease in diabetic patients Fact or fiction? Circulation 57 133 1978
9. Waller B F, Palumbo P J Lie J T, and Roberts W C Diabetes mellitus an accelerator of coronary athero sclerosis only when onset is before age 46 A necropsy study of 1 172 diabetic coronary arteries and 844 control coronary arteries (Abstr) Am J Cardiol 43 436 19 9
10. Favaloro R G Direct myocardial revascularization A ten year journey Myths and realities, Am J Cardiol 43 109 1979
11. Sones F M Jr and Shirey E K Cine coronary arteriography Mod Concepts Cardiovasc Dis 31 735 196?
12. Ganz W Donoso R Marcus H R Forrester J S and Swan H J C A new technique for measurement of cardiac output by thermodilution in man Am J Cardiol 27 392 1971
13. Herman M V Heinle R A Klein M D and Gorlin R Localized disorders in myocardial contraction Asynergy and its role in congestive heart failure N Engl J Med 277 ? ? 1967
14. Snedecor G W and Cochran G W Statistical meth od Ames Iowa 1967 Iowa University press
15. Liebow I M and Hellerstein H K Cardiac complica tion in diabetes mellitus Am J Med 7 660 1949
16. Bell E T A A post mortem study of vascular disease in diabetes Arch Pathol 53 444 1952
17. Kannel W B Hjortland M and Castelli W P Role of diabetes in congestive heart failure the Framingham study Am J Cardiol 34 29 1974
18. Clawson B J and Bell E T Incidence of fatal coronary disease in non diabetic and diabetic persons, Arch Pathol 48 105 1949
19. Partamian J O and Bradley R F Acute myocardial infarction in 258 cases of diabetes immediate mortality and five years survival N Engl J Med 273 455 1965
20. Bradley R F and Bryfogle J W Survival of diabetic patients after myocardial infarction Am J Med 20 ?0 19 6
21. Blumenthal H T Olex M, and Goldenburg S A study of lesions of the intramural coronary artery branches in diabetes mellitus Arch Pathol 70 27 1960
22. Pearse M B Bulloch R T and Kizziar J C Myocar dial small vessel disease in patients with diabetes mellitus (Abstr) Circulation 48(Suppl IV) 6 1973
23. Sohar E Ravid M Ben-Shaul Y Reshes T and Gasni J Diabetic fibrillosis Am J Med 49 64 19 0
24. Regan T J Ettinger P O Khan M I Jesrani M Y Lyons M M Oldewurtel H A and Weber M Altered myocardial function and metabolism in chronic diabetes mellitus without ischemia in dogs Circ Res 35 2?2 1974

Table II Patients No 4 to 9 clinical and electrophysiological data

Case no	Age (years)	Sex	Diagnosis	ECG	Angiography	Previous treatment
4	23	M	Congestive cardiomyopathy	LAHB LVH	Left lateral ventricular aneurysm	Propranolol Digoxin Procainamide Diphenylhydantoin, Disopyramide Amiodarone Aprindine with Quinidine Ajmaline Mexiletine
5	52	M	Coronary artery disease	IWMI	Stenosed arteries RCA (100%) LAD (60%) 2nd diagonal (100%) segment V akinetic	Disopyramide Ajmaline Procainamide Aprindine Tocainide moxaprindine Mexiletine Amiodarone
6	54	M	Coronary artery disease	AWMI IWMI	Stenosed arteries RCA (60%) LAD (70%) aneurysm of segments II III IV V	Mexiletine Moxaprindine
7	47	M	Coronary artery disease	PIWMI	Stenosed arteries RCA (100%) Cx (60%) Sacciform aneurysm of segment V	Disopyramide Aprindine
8	55	M	Coronary artery disease	EAMI	Apical and left anterior aneurysm demonstrated by gated pool scans	Aprindine Moxaprindine
9	60	M	Coronary artery disease	AWMI IWMI	Thrombosis of RCA and LAD aneurysm of segments III IV and V	Disopyramide Lorcainide Mexiletine

RBBB right bundle branch block LBBB left bundle branch block RAD right axis deviation LAD left axis deviation RCA right coronary artery LAD left anterior descending artery Cx circumflex artery LAHB left anterior hemiblock LVH left ventricular hypertrophy MI myocardial infarction IW inferior wall PIW posteroinferior wall EA extensive anterior CL cycle length morphol. morphology
prehospital treatment unknown

mexiletine and is totally asymptomatic (follow up 9 months) Patient No 7 received no antiarrhythmic therapy after his operation Five months later he presented a recurrence of his rhythm disorders and a control left ventricular angiogram demonstrated the reappearance of a voluminous inferior aneurysm the patient was reoperated upon and died during surgery Patients No 3 4 8 and 9 are all presently asymptomatic In one of them (patient No 3) the development of gastrointestinal discomfort at 5 weeks led to the replacement of mexiletine by another class I agent (aprindine 100 mg/day) Patient No 4 still presents on ambulatory monitoring rare bouts of ventricular tachycardia which show a rate of 100 beats/minute and which are not perceptible to the patient

Discussion

The pharmacological treatment of recurrent life threatening ventricular tachycardia constitutes a difficult problem Most investigators agree with Zipes that it may be as naive to think that one antiarrhythmic drug will be effective for all patients as it is to think that one antibiotic will cure all infections

In this respect it seems logical to admit that at least in difficult cases the administration of an association of drugs may become necessary

Intracellular recordings on atrial and ventricular

Table I Clinical features of the first three cases treated by mexiletine + amiodarone

Case no	Age (years)	Sex	Diagnosis	Arrhythmias	Previous treatment IV or oral
1	64	Male	3 attacks of myocardial infarction left and right ventricular failure	VF VT multifocal VPBs	Lidocaine Diphenylhydantoin Practolol Procainamide Mexiletine digoxin Prazosin
2	64	Male	Hypertensive heart disease diabetes mellitus sick sinus syndrome congestive heart failure (scintigraphy posteroinferior hypofixation left ventricular enlargement)	AF VF multifocal VPBs	Xylocaine Disopyramide Practolol Mexiletine Digoxin
3	62	Male	2 attacks of posteroinferior myocardial infarction residual angina (aorto coronary bypass grafts on the anterior descending and circumflex arteries)	VT VPBs	Xylocaine Disopyramide Propranolol Mexiletine

plus DC shock whenever necessary
AF atrial fibrillation VT ventricular tachycardia VF ventricular fibrillation VPB ventricular premature beats.

The treatment was given as follows During the first two days mexiletine and amiodarone were perfused intravenously at a dose of 1 000 mg and 1,500 mg per 24 hours respectively Simultaneously amiodarone was also given orally at a dose of 600 mg per 24 hours From day 3 onwards the intravenous administration was interrupted and both drugs were continued orally at a dose of 600 mg daily

Results

In the first three cases the association of amiodarone and mexiletine resulted in total suppression of the tachycardic episodes within the first three days after initiation of treatment No electrophysiological study was performed in those patients who could be released from the intensive care unit to a normal ward after two weeks of therapy

In the last six cases episodes of ventricular tachycardia could easily be triggered by programmed electrical stimulation The morphology of QRS and cycle length during tachycardia are indicated in Table II In all but one patient (No 4) the cycle length of the electrically induced tachycardia was shorter than the cycle length of the spontaneous epidoses even when the QRS morphology was identical In addition in five out of the six instances it was possible to induce during ventricular programmed stimulation tachycardic epidoses showing different QRS morphologies and cycle lengths This pleiomorphism was associated with the existence of large aneurysmal or akinetic areas as observed at left ventricular angiography or blood pool scans After five days of treatment no tachycardia could be elicited in patients No 6 7 8 and 9 When the six subjects were retested on day 7 none developed ventricular tachycardia

The follow up of these patients is still rather short (Table III) Patients No 1 and 2 remained *free from ventricular tachycardia but died after 2* and 5 months from intractable heart failure One of them (patient No 2) who was known to have a sick sinus syndrome developed under the influence of treatment a severe symptomatic bradycardia which justified implantation of a pacemaker Another patient (No 6) was lost to follow up soon after his release from hospital He was brought dead to the emergency department 4 1/2 months later and we were not able to find out whether he had continued his treatment in the meantime This patient had had a large anterior myocardial infarction He had a cardiomegaly and a large aneurysmal formation Two patients (No 5 and 7) who had suffered no relapse of tachycardia underwent cardiac surgery at 6 weeks (*triple aortocoronary bypass graft*—*patient* No 5) and 8 weeks (aneurysmectomy—patient No 7) respectively Patient No 5 presently remains on

Table III Follow up

Case No	Duration of follow up (months)	Description of outcome
1	2	Died from intractable heart failure
2	5	Died from intractable heart failure
3	9	At 5 weeks gastrointestinal discomfort Replacement of mexiletine by aprindine (100 mg daily) Asymptomatic
4	5	Asymptomatic Rare bouts of slow VT depicted at Holter monitoring
5	9	Triple aortocoronary bypass grafts at 8 weeks Asymptomatic
6	4½	Lost to follow up Sudden death
7	8	Aneurysmectomy at 6 weeks No antiarrhythmic therapy after operation Recurrence of VT at 7 months when administration of amiodarone and mexiletine was reinstated Documented recurrence of left ventricular aneurysm Died at surgery
8	4	Asymptomatic
9	6½	Asymptomatic
	58	

whereas no arrhythmia could be triggered in any of them after seven days of administration

The short term results obtained with the association of amiodarone with mexiletine were surely encouraging since spontaneous recurrence of the arrhythmia was prevented in all nine cases After one week of treatment no ventricular tachycardia could be started by electrophysiologic testing in the six cases in whom tachycardic episodes had easily been initiated prior to the initiation of therapy

The long term follow up reflects the over all rather poor prognosis of patients suffering from this type of rhythm disorder Patient No 3 who died suddenly presented with all the markers of the highest risk group among postinfarction patients [6] He had had a large anterior transmural myocardial infarction He had a cardiomegaly an aneurysmal formation and clinical and angiographic evidence of left ventricular dysfunction of a severe degree His demise was not unexpected and we do not even know whether he continued his treatment after his release from the hospital

The other two subjects who died also had a guarded prognosis from the start They had shown signs of severe right and left heart failure in the intensive care unit In spite of the disappearance of their arrhythmia they soon died in intractable cardiac decompensation It is impossible in these cases to rule out a deleterious influence of the antiarrhythmic treatment on cardiac function In two patients the drug association permitted us to perform safely the invasive investigations which preceded a surgical procedure One of these subjects is now doing well the other died after a recurrence of his left ventricular aneurysm and simultaneously of his rhythm disorder He was receiving no antiarrhythmic therapy at the time of his relapse The other patients remain asymptomatic even if one of them still shows bouts of slow ventricular tachycardia on ambulatory monitoring

In this study the efficacy of the drug cover was assessed by repeated electrophysiologic testing Although the technique still deserves further evaluation in long term follow up studies it is thought to provide a good and fast way of selecting the drug regimen which should best protect the patients Several recent reports suggest that the results yielded by this method correlate reasonably well with the effectiveness of long term suppressive therapy [9,14] Although the follow up of our patients is relatively short the present observations are in agreement with this opinion

This report admittedly lacks the strong impact of a controlled study However all practitioners realize the difficulty of controlled studies in patients with life threatening arrhythmias In this situation ethical problems almost always prevent the application of a rigourous scientific methodology Nonetheless it is for this very group of patients that effective antiarrhythmic therapy is most needed We believe that the present data provide sufficient evidence to indicate that the association of a class I with a class III agent may be of interest in the therapy of individuals with refractory recurrent ventricular tachyarrhythmias It is apparent however that

Spontaneous VT			*Induced VT*		
Morphol.	*Axis*	*CL (msec)*	*Morphol.*	*Axis*	*CL (msec)*
RBBB	RAD	220	RBBB	RAD	[illegible]
			LBBB	LAD	[illegible]
RBBB	RAD	240	RBBB	RAD	[illegible]
LBBB	LAD	400	RBBB	RAD	430
			LBBB	LAD	400
RBBB	RAD	550	RBBB	RAD	430
			LBBB	LAD	400
RBBB	RAD	360	RBBB	RAD	[illegible]
			LBBB	LAD	150
RBBB	RAD	240	RBBB	RAD	[illegible]
			LBBB	LAD	230

lar muscle cells have indicated that mexiletine has, according to Vaughan Williams classification,[3] a typical class I action causing a significant reduction of maximum rate of depolarization with no change of resting potential. Like lignocaine, mexiletine shortens the action potential in all cardiac tissues but this effect is particularly conspicuous in that portion of the conduction system which has the longest action potential duration. As a result of this differential effect, action potential duration becomes uniformly short. Some investigators have suggested that the greater uniformity of action potential duration may contribute to the antiarrhythmic action of the drug. Vaughan Williams has questioned this opinion.[3] He believes to the contrary that the shortening of action potential might be arrhythmogenic and expresses the feeling that the antiarrhythmic effect of mexiletine can be attributed to its class I action and that this exists in spite of the shortening of action potential. In view of this, one is tempted to wonder whether there might not exist a synergistic action between class I agents and substances which, like amiodarone, prolong the action potential duration (class III of Vaughan Williams classification). This assumption prompted us to use the association of mexiletine and amiodarone in our patients.

It should be pointed out that our work was not designed to try and demonstrate that the association of amiodarone with mexiletine is clinically superior to either drug given alone. The purpose of this paper is simply to report on the results obtained with this double drug regimen in patients with life-threatening refractory ventricular tachyarrhythmias. It is worthy of note, however, that seven of our patients had previously received mexiletine given singly; two others had received amiodarone. The treatment had been judged unsatisfactory either because of unresponsiveness or because of the appearance of untolerable side effects.

The mode of administration was selected according to the pharmacokinetics of each of the drugs which were administered. Mexiletine is known to require a loading dose on the initiation of chronic oral therapy.[6] This justified the parenteral administration during the first 2 days. No plasma level of mexiletine could unfortunately be obtained to demonstrate that a steady state plasma concentration within the therapeutic range was achieved. The pharmacokinetics of amiodarone are less well known and its investigation has always been hampered by the absence of a reliable method for drug plasma level determinations. It is known on a clinical basis that several days of treatment by amiodarone at 600 mg per day are required for the full antiarrhythmic efficacy to become manifest.[7] This delay is thought to reflect the time which is necessary to build up sufficient concentrations of the drug within the myocardial cells. Amiodarone was therefore used intravenously during the first two days of treatment with the hope that this would shorten this delay and improve the reliability of drug cover. It is likely, however, that the particular characteristics of amiodarone's clinical pharmacology explains why two patients were not yet totally protected after five days of treatment

Table III Follow up

Case No	Duration of follow up (months)	Description of outcome
1	2	Died from intractable heart failure
2	5	Died from intractable heart failure
3	9	At 5 weeks gastrointestinal discomfort Replacement of mexiletine by aprindine (10[illegible] mg daily) Asymptomatic
4	5	Asymptomatic Rare bouts of slow VT depicted at Holter monitorin[illegible]
5	9	Triple aortocoronary bypass grafts at 8 weeks Asymptomatic
6	4½	Lost to follow up Sudden death
7	8	Aneurysmectomy at 6 weeks No antiarrhythmic therapy after operation. Recurrence of VT at 7 months when administration of amiodarone and mexiletine was reinstated Documented recurrence of left ventricular aneurysm Died at surgery
8	4	Asymptomatic
9	6½	Asymptomatic
	5.8	

whereas no arrhythmia could be triggered in any of them after seven days of administration

The short term results obtained with the association of amiodarone with mexiletine were surely encouraging since spontaneous recurrence of the arrhythmia was prevented in all nine cases After one week of treatment no ventricular tachycardia could be started by electrophysiologic testing in the six cases in whom tachycardic episodes had easily been initiated prior to the initiation of therapy

The long term follow up reflects the over all rather poor prognosis of patients suffering from this type of rhythm disorder Patient No 3 who died suddenly presented with all the markers of the highest risk group among postinfarction patients[8] He had had a large anterior transmural myocardial infarction He had a cardiomegaly an aneurysmal formation and clinical and angiographic evidence of left ventricular dysfunction of a severe degree His demise was not unexpected and we do not even know whether he continued his treatment after his release from the hospital

The other two subjects who died also had a guarded prognosis from the start They had shown signs of severe right and left heart failure in the intensive care unit In spite of the disappearance of their arrhythmia they soon died in intractable cardiac decompensation It is impossible in these cases to rule out a deleterious influence of the antiarrhythmic treatment on cardiac function In two patients the drug association permitted us to perform safely the invasive investigations which preceded a surgical procedure One of these subjects is now doing well the other died after a recurrence of his left ventricular aneurysm and simultaneously of his rhythm disorder He was receiving no antiarrhythmic therapy at the time of his relapse The other patients remain asymptomatic even if one of them still shows bouts of slow ventricular tachycardia on ambulatory monitoring

In this study the efficacy of the drug cover was assessed by repeated electrophysiologic testing Although the technique still deserves further evaluation in long term follow up studies it is thought to provide a good and fast way of selecting the drug regimen which should best protect the patients Several recent reports suggest that the results yielded by this method correlate reasonably well with the effectiveness of long term suppressive therapy Although the follow up of our patients is relatively short, the present observations are in agreement with this opinion

This report admittedly lacks the strong impact of a controlled study However all practitioners realize the difficulty of controlled studies in patients with life threatening arrhythmias In this situation ethical problems almost always prevent the application of a rigourous scientific methodology Nonetheless it is for this very group of patients that effective antiarrhythmic therapy is most needed We believe that the present data provide sufficient evidence to indicate that the association of a class I with a class III agent may be of interest in the therapy of individuals with refractory recurrent ventricular tachyarrhythmias It is apparent however that

this treatment will not be able to protect patients at highest risk especially those in whom the proportion of functionally viable myocardium is too small It may however be most helpful in less severe cases or during the period which precedes a surgical procedure consisting of coronary bypass grafting or aneurysmectomy

Summary

A combined mexiletine and amiodarone treatment was applied in nine cases with recurrent *refractory ventricular tachycardia* During the first two days of treatment mexiletine and amiodarone were perfused intravenously at a dose of 1 000 mg and 1 500 mg per 24 hours respectively Simultaneously amiodarone was also given orally at a dose of 600 mg per 24 hours From the third day onwards the intravenous administration was interrupted and both drugs were continued orally at a dose of 600 mg daily

The first three patients were very critically ill and had had at least five episodes of ventricular tachycardia per 24 hours during the last 10 days in the intensive care unit The treatment resulted in total suppression of the tachycardic episodes within three days after initiation of therapy

In the remaining six cases ventricular tachycardia was easily initiated by programmed electrical stimulation of the heart No arrhythmia could be elicited by repeated testing on the seventh day of treatment

The mean follow up period was 6 months Two patients with poor left ventricular function died in intractable heart failure Another one died suddenly 4 ½ months after his release from the hospital He had a large aneurysm and whether he continued his treatment is unknown A fourth patient had an aneurysmectomy he suffered a recurrence and died at his second operation All the others presently remain asymptomatic

The association of a class I (mexiletine) with a class III (amiodarone) agent is theoretically attractive for the treatment of refractory ventricular arrhythmias

The present findings corroborate this hypothesis but show that this association is not able to protect individuals with severe underlying myocardial damage

The authors would like to express their gratitude to Mrs B Vervier and F Courtois for their helpful secretarial and technical assistance

REFERENCES

1 Waleffe A Bruninx P Mary Rabine L and Kulbertus H E Effects of tocainide studied with programmed electrical stimulation of the heart in patients with reentrant arrhythmias Am J Cardiol 43 092, 1979

2 Zipes D Symposium on new aspects of antiarrhythmic therapy Introduction Miles to go Am J Cardiol 41 975 1978

3 Vaughan Williams E M Mexiletine in isolated tissue models Postgrad Med J 53(Suppl 1) 30 1977

4 Wittig J H Harrison L A, and Wallace A J Electrophysiological effects of lidocaine on distal Purkinje fibers of canine heart Am Heart J 86 69 1977

5 Vaughan Williams, E M *in* Panel Discussion Postgrad Med J 53(Suppl 1) 46 1977

6 Paalman A C A Roos, J C Siebelink J, and Dunning A J Development of a dosage scheme for simultaneous intravenous and oral administration of mexiletine, Postgrad Med J 53(Suppl. 1) 128 1977

7 Zipes, D P, and Troup P J New antiarrhythmic agents amiodarone aprindine disopyramide ethmozin mexiletine tocainide verapamil Am J Cardiol 41 1005 1978

8 Kennel W B Sorlie P, and MacNamara P M Prognosis after initial myocardial infarction the Framingham study Am J Cardiol 44 58 1979

9 Winkle R A Alderman E L, Fitzgerald, J W, and Harrison D C Treatment of symptomatic ventricular tachycardia Ann Intern Med 85 1 1976

10 Wu D Windham C R Denes, P Amat y Leon F, Miller R M Dhingra R C and Rosen K M Chronic *electrophysiologic study in patients with recurrent* paroxysmal tachycardia a new method for developing successful oral antiarrhythmic therapy *in* Reentrant Arrhythmias, Mechanisms and Treatment H E Kulbertus, ed Lancaster 1977 MTP

11 Fisher J D, Cohen A L, Mehra R, Actschuler H, Escher D J W and Furman S Cardiac pacing and pacemakers II Serial electrophysiologic pharmacologic testing for control of recurrent tachyarrhythmias, Am Heart J 83 658 1977

12 Horowitz L N Josephson A E, Farshidi A, Spielman S R Michelson E L, and Greenspan A M Recurrent sustained ventricular tachycardia. 3 Role of the electrophysiologic study in selection of antiarrhythmic regimens, Circulation 58 986 1978

13 Mason J W and Winkle R A Electrode catheter arrhythmia Induction in the selection and assessment of antiarrhythmic drug therapy in recurrent ventricular tachycardia Circulation 58 971 1978

14 Benditt D G, Gallagher J J, and Pritchett E L C Recurrent ventricular tachycardia in man evaluation of antiarrhythmic drug therapy by programmed intracardiac stimulation *in* Management of Ventricular Tachycardia Role of Mexiletine Sandoe E, Julian D G, and Bell J W, Eds. Amsterdam Oxford 1978 Excerpta Medica, p 497

Table II Hemodynamic and angiographic findings

lectrocardiogram (QRS)	Left ventricular hypertrophy			Normal			Significance
	Mean	No	Percent	Mean	No	Percent	
res (mm. Hg)							
ta (mean)	103 ± 20			101 ± 15			NS
ventricular systolic	151 ± 34			143 ± 25			NS
ventricular diastolic	20 ± 8			12 ± 6			p<[illegible]
entricular							
-diastolic volume (mL/m)	80 ± 28			66 ± 22			p<[illegible]
tion fraction	0.55 ± 0.20			0.64 ± 0.11			p<[illegible]
tractile pattern, abnormal		34	60		26	46	NS
regurgitation		14	25		7	12	NS
ary artery disease							
le vessel disease		9	16		15	26	NS
ble vessel disease		21	37		24	42	NS
le vessel disease		27	47		18	32	NS
left coronary disease		7	12		5	9	NS
l coronary artery score	9.8 ± 2.8			9.2 ± 3.0			NS

alues given with ± 1 standard deviation.
not significant No = number of patients.

and 30% of patients in the LVH ECG and normal QRS-ECG group respectively .001) In all instances the hypertension was lered mild with the systemic diastolic pres anging from 90 to 100 mm Hg At the time of ation (Table II) there was no significant ence when the groups were compared for aortic pressures or the left ventricular ic pressures Cardiomegaly was significantly .005) more frequent in the LVH ECG (49% vs 4%)

hemodynamic and angiographic findings in two groups is shown in Table II LVH ECG demonstrated evidence of greater left ven r dysfunction as evidenced by end-diastolic res end-diastolic volumes and ejection ns Fig 1 shows that an elevated end lic pressure (> 12 mm Hg) was observed in patients in the LVH ECG group compared in the normal QRS ECG group An abnor nd-diastolic volume (> 100 ml/m) and n fraction (< 0.5) was found in 21% and espectively in the LVH ECG group com to 4% and 16% in the normal QRS ECG Generalized hypokinesia of the left ventri angiographic study was observed in six s in the LVH ECG group while no patient normal QRS ECG group demonstrated this . Comparison of the e ents of the coro tery disease as reflec ed by the number of involved the frequen f main left coro rtery disease and to a coronary artery score revealed no significant differences (Tab II)

LVH ECG group hypertension vs no hyperten sion A comparison of the 43 hyperten patients in the LVH ECG group with the rem ing 14 nonhypertensive patients revealed 2% of the hypertensive patients to be female compar to only 8% of the nonhypertensive patients The clinical profile of these two subgroups of patien in the LVH ECG group revealed no signific differences The Romhilt Estes point score fo left ventricular hypertrophy was similar in the hypertensive and nonhypertensive pati (6.1 ± 2.3) Mean aortic pressure was a expected higher ($p < 0.05$) in the hyperten patients (107 ± 20 mm. Hg vs. 95 ± 12 mm Hg The LV end-diastolic pressures, volumes, an ejection fractions for both subgroups of patien with left ventricular hypertrophy revealed n significant differences. Generalized hypokinesi of LV contraction was observed in 7% of patien with hypertension compared to 21% without. The number of vessels involved and total corona score for both LVH ECG subgroups revealed n significant difference however the frequency of main left coronary artery disease was significan ly ($p < 0.05$) higher in the subgroup witho hypertension (29% vs. 7%)

ECG LVH group—LAE vs no LAE. The patients in the LVH ECG group had atrial en lation all also had cardiomegaly abnormal end diastolic pressures volumes and ejection fr

Table I Clinical profile

Electrocardiogram (QRS)	*Left ventricular hypertrophy*			*Normal*			*Significance*
	Mean	*No*	*Percent*	*Mean*	*No*	*Percent*	
Number of patients		57			57		
Male/Female		45/12			45/12		
Age (yrs)	61.5 ± 8			61.5 ± 9			
Duration of symptoms (yrs)	1.7 ± 1.1			1.4 ± 0.9			NS
Congestive heart failure		14	25		0	0	$p < 0.005$
Hypertension		43	5		17	30	$p < 0.001$
Diabetes mellitus		13	23		9	16	NS
Cigarette smokers		21	37		23	40	NS
Cardiomegaly		28	49		2	4	$p < 0.005$

Mean values given with ± 1 standard deviation.
NS = not significant No = number of patients yrs. = years.
Duration of angina pectoris.

therapy accompanied by an elevated (> 120 mg dl) fasting blood sugar Radiologic evaluation and interpretation for cardiomegaly was performed by a radiologist

Electrocardiographic QRS voltage limits suggesting *left ventricular hypertrophy* were based on accepted criteria[1] Twelve lead standard electrocardiograms taken on all patients were reviewed by at least two of the authors and a diagnosis of left ventricular hypertrophy was made on the basis of a combination of several but not necessarily all of the following electrocardiographic findings S wave in Lead V_1 plus R wave in Leads V_5 or V_6 > 35 mm R wave in Lead aV > 11 mm R wave in Lead I plus S wave in Lead III > 25 mm or R wave in Lead aV_F > 20 mm ST T segment and T wave deflection (with or without digitalis) in a direction opposite to the main QRS was noted Left atrial enlargement (LAE) was diagnosed if the terminal negativity of the P wave in Lead V was 1 mm or more in depth accompanied by a duration of 40 msec or more The Romhilt Estes point score system for ECG diagnosis of left ventricular hypertrophy was also utilized[1] The ECGs in the 57 control patients (normal QRS ECG group) were in all instances reviewed by two readers who agreed that the QRS was normal

The various *methods utilized* to evaluate patients in this study have been previously described in detail[1] Essentially all patients underwent right and left heart catheterization as well as left *ventricular and selective coronary* angiography Left ventricular angiograms were performed to evaluate wall motion and to determine end diastolic volumes and ejection fractions The left ventricular contractile pattern was determined by superimposing the end-diastolic and end systolic silhouette of the left ventricular angiogram utilizing criteria previously described Selective coronary arteriograms were reviewed to determine the number of major arteries (left anterior descending circumflex and right coronary artery) involved with significant *disease—i e narrowing of an artery* by more than 50% of the wall lumen The severity of involvement of each of the major coronary arteries was graded on the basis of a score from 0 to 6 as defined by Bruschke[4] *The total coronary score* was the sum of the scores of the three major coronary arteries Involvement of the main left coronary artery was considered separately All information was *tabulated and evaluated by* standard statistical methods

Results

LVH ECG group vs normal QRS ECG group The clinical profile of patients meeting electrocardiographic criteris for left ventricular hypertrophy (LVH ECG group) is shown in Table I and is compared with 57 patients matched for both age and sex but having a normal QRS complex (normal QRS ECG group) The duration of symptoms in these two groups of patients were not significantly different and in all instances the patients were evaluated because of angina pectoris However 25% of the patients in the LVH ECG group had a history of congestive heart failure compared to none in the normal QRS ECG group ($p < 0.005$) Hypertension was noted

Table III Hemodynamic and angiographic findings as related to atrial enlargement

	Left atrial enlargment			*No left atrial enlargment*			
	Mean	*No*	*Percent*	*Mean*	*No*	*Percent*	Signifi-
Number of patients		30			24		
Left ventricular							
End diastolic pressure (mm Hg)	16 ± 9			13 ± 5			NS
End-diastolic volume (ml/m²)	83 ± 31			70 ± 17			NS
Ejection fraction	0.50 ± 0.18			0.64 ± 0.17			$p<0.0$[illegible]
Abnormal (<0.5)		13	43		3	13	$p<0.0$[illegible]
Contractile pattern abnormal		22	73		9	3[illegible]	$p<0.0$[illegible]
Coronary artery disease							
Single vessel disease		1	3		7	29	$p<0.0$[illegible]
Double vessel disease		16	53		4	17	$p<0.0$[illegible]
Triple vessel disease		13	43		13	[illegible]	NS
Main left coronary disease		2	7		4	17	N[illegible]
Total coronary artery score	10 ± 3			9 ± 3			

LVH) without evidence of a prior transmural myocardial infarction or intraventricular conduction disturbance These patients represent only 3 9% of our population of patients with ischemic heart disease seen during a four year period Conclusions based on this study are thus limited by the patient referral and the criteria for selection into the study

This study was motivated by the prospective epidemiological work of Kannel and associates [11] and Chiang and co workers In the Framingham study a threefold increased risk of developing coronary artery disease was noted in the presence of ECG LVH even after adjustment for the effect of coexisting hypertension ECG LVH was associated with an increased risk of all clinical manifestation of coronary artery disease and in particular with a coronary death In 40% with ECG LVH death occurred as the initial coronary event Combining the experience from both Framingham and Albany[9] indicated that ECG LVH and the presence of another coronary risk factor strongly suggested the presence of occult coronary artery disease Men with ECG LVH had a fivefold increase in risk of sudden death[9] and 29% presented with sudden death compared to 10% among those without this electrocardiographic abnormality Thus the Framingham study suggested that ECG LVH was a marker of latent coronary artery disease and was associated with an ominous prognosis In the Tecumseh Study [10] the six year incidence of sudden death (per 1 000 population) in those with ECG LVH was 48, compared to 2[illegible] in those with a normal electrocardiogram and almost comparable to subjects demonstrating ventricular premature be[illegible] (61 of 1 000 population) In a study by Dison a[illegible] associates [19] ECG LVH in patients having co[illegible] nary artery disease was associated with a sig[illegible] cant ($p < 0.005$) linear correlation for a cardi[illegible] death

The present study demonstrates both clini[illegible] and hemodynamic findings of significa[illegible] impaired left ventricular function in a large nu[illegible] ber of patients with ECG LVH This was read[illegible] evident in comparison to age sex matched co[illegible] trols also referred because of symptomatic co[illegible] nary artery disease but without ECG LVH [illegible] both groups of patients (ECG LVH and ECG normal QRS) there was no significant differe[illegible] in the duration of symptoms and no patient ha[illegible] clinical history of electrocardiographic evide[illegible] of a prior myocardial infarction The difference in left ventricular function (Fig 1) between the two groups of patients could not be explained [illegible] the basis of the severity of the coronary arte[illegible] disease (Table I) Hypertension as expected w[illegible] present in three quarters of the patients [illegible] ECG LVH and no doubt contributed to the [illegible] ings in the present study The combination [illegible] hypertension and ECG LVH was present in [illegible] patients In our experience[15] 30% of pati[illegible] patients In our experience[15] 30% of patients evaluated with coronary artery disease have [illegible] documented hypertension Thus of the [illegible] patient population reviewed (1 46? patients) [illegible] had hypertension but only 10% had ECG LV[illegible] Hypertension in combination with corona[illegible] artery disease could well explain the high [illegible] dence of left ventricular dysfunction observed [illegible] the present study in our ECG LVH group H[illegible]

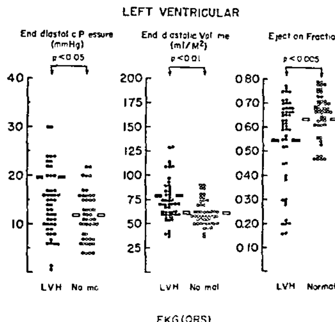


Fig 1 Parameter of left ventricular function evaluated in study patients *Each point* represents the value of an individual patient with *the horizontal bar* being the mean for each group

tions Of the remaining 54 patients in normal sinus rhythm 24 had normal P wave contours while 30 had left atrial enlargement by ECG Evaluating these two subgroups (left atrial enlargement present or absent) with left ventricular hypertrophy revealed no significant differences in their clinical profile except for a greater frequency ($p < 0.05$) of cardiomegaly in the subgroup with left atrial enlargement (59% vs 29%) The left ventricular hemodynamics and angiographic findings in these two subgroups with left ventricular hypertrophy are shown in Table III Of note is the significantly ($p < 0.01$) lower ejection fraction in the subgroup with left atrial enlargement An abnormal ejection fraction (< 0 5) was present in 43% with left atrial enlargement by ECG compared to 13% with normal P waves ($p < 0.025$) Furthermore 73% of patients with such atrial enlargement had an abnormal left ventricular contractile pattern compared to 38% without atrial enlargement ($p < 0.01$) Single vessel coronary disease was more frequent (29% vs 3%) in the subgroup without atrial enlargement ($p < 0.01$) The frequency of main left coronary artery disease was 7% and 17% respectively in those with and without left atrial enlargement

ECG LVH group—ST T wave changes vs normal ST T wave Finally an evaluation of the LVH ECG group on the basis of ST segment and T wave changes revealed that of the 44 patients with such changes 57% had cardiomegaly compared to 23% in those without ST and T wave abnormalities ($p < 0.05$) Congestive heart failure was also more frequent (30% vs 8%) in those with ST segment and T wave changes Left ventricular hemodynamics revealed no significant differences when evaluated on the basis of the presence or absence of ST segment and T wave Generalized hypokinesia was present in six patients with ST and T wave abnormalities In all of these the left ventricular end diastolic pressures volumes and ejection fractions were abnormal The severity of the coronary artery disease revealed no significant differences when those with ST segment and T wave abnormalities were compared to those with normal ST and T waves

No relationship was observed between the Romhilt Estes point score of left ventricular hypertrophy and any parameter of left ventricular function—i e end-diastolic pressure volume ejection fraction or contractile pattern Similarly the severity of coronary artery disease could not be related to the LVH point score

Discussion

The present report reviewed a select subset of patients referred because of angina pectoris not readily controlled by medical management The criteria for selection was documented coronary artery disease and an electrocardiogram demonstrating left ventricular hypertrophy (ECG

left ventricular dysfunction (Table III) Prior studies by Rios and co workers[1 36] demonstrated that left atrial enlargement in patients with coronary artery disease is correlated with left ventricular dysfunction Thus, left atrial enlargement in patients with coronary artery disease was associated with a higher left ventricular end diastolic pressure and increased frequency of left ventricular contractile abnormalities Further it was observed[15 36] that left atrial enlargement was also associated with increased severity of coronary artery disease, a finding not confirmed in our patient population with ECG LVH All three patients with ECG LVH combined with atrial fibrillation had severe left ventricular dysfunction Evaluating ECG LVH further on the basis of abnormal ST segments and T waves was not found helpful in identifying a subgroup with either left ventricular dysfunction or more severe coronary artery disease

From the observations it is concluded that ECG LVH in patients with ischemic heart disease defines a group of patients with an increased frequency of left ventricular dysfunction especially if ECG left atrial enlargement is also present This finding cannot be explained on the basis of prior myocardial infarction No patients had a clinical history or electrocardiographic evidence of such infarction The presence of myocardial hypertrophy and coronary artery disease would certainly bring on a disparity between oxygen demand and supply which, if protracted, could result in ischemic myocardial fibrosis The stimulus for myocardial hypertrophy be it hypertension or chronic ischemia results in increased muscle mass receiving a limited oxygen supply The subgroup of patients with ECG LVH and no prior history of hypertension presented with an excess frequency of main left coronary artery disease On the basis of these findings as well as prior clinical observation it certainly appears warranted that patients with ECG LVH and suspected coronary artery disease should undergo full evaluation in order to define the coronary anatomy and left ventricular function

Summary

The present investigation defines left ventricular function and coronary artery anatomy in a group of patients with electrocardiographic evidence of left ventricular hypertrophy (ECG LVH) and documented coronary artery disease The ECG LVH group consisted of 57 pa[illegible] who were matched with age/sex controls [illegible] patients were evaluated because of angina pec[illegible]ris and no patient had a history or ECG eviden[illegible] of prior myocardial infarction The duration [illegible] symptoms in both groups was not significa[illegible] different Hypertension (75% vs 30%) conges[illegible] heart failure (25% vs 0%) and cardiomegaly ([illegible] vs 4%) were significantly more frequent in t[illegible] ECG LVH group The ECG LVH group demo[illegible]strated greater left ventricular dysfunction [illegible] evident in a higher left ventricular end-diasto[illegible] pressures (20 ± 8 vs 12 ± 9 mm Hg) e[illegible] diastolic volumes (80 ± 28 vs 66 ± 2? ml/m[illegible] and lower ejection fractions (0 55 ± 0 20 [illegible] 0 64 ± 0 17) The severity of the coronary art[illegible] disease as reflected by the number of ves[illegible] involved and total coronary score revealed [illegible] significant group differences The ECG L[illegible] group was further divided based on ECG [illegible] atrial enlargement (LAE) Such evidence of L[illegible] was associated with a higher frequency (p < 0[illegible] of cardiomegaly (59% vs 29%) and a significan[illegible] (p < 0 01) lower ejection fraction (0.50 ± [illegible] 0 64 ± 0 17), as well as higher freq[illegible] (p < 0 005) of an abnormal contractile patt[illegible] (76% vs 37%) Evaluation of the ECG LVH gr[illegible] with the Romhilt Estes point score for the L[illegible] or the presence of abnormal ST segments an[illegible] waves revealed no significant difference in [illegible] ventricular function Patients with hyperten[illegible] compared to those with no hypertension reve[illegible] no differences in LVH point score or left vent[illegible]ular function however, main left coronary ar[illegible] disease was significantly (p < 0 05) more frequ[illegible] in the ECG LVH subgroup with no hyperten[illegible] (29% vs 7%)

It is concluded that ECG LVH in patients [illegible] coronary artery disease defines a group [illegible] patients with increased frequency of left ve[illegible] ular dysfunction especially when associated [illegible] LAE Furthermore such ECG findings in [illegible] presence of ischemic heart disease defines a [illegible] group of patients with an excessive frequenc[illegible] main left coronary artery disease These obse[illegible] tions may in part explain the poor progr[illegible] previously described from epidemiological stu[illegible] of patients with ECG LVH and coronary ar[illegible] disease

The authors wish to thank Brenda Hamby and Da[illegible] Horowitz for their assistance given in the preparation of [illegible] manuscript

ever in a review of our data it was observed that hypertensive patients in our control (normal QRS) group were not characterized by left ventricular dysfunction Thus the finding of LVH on the electrocardiogram in a patient with ischemic heart disease suggests that such a finding may be a marker for left ventricular dysfunction

Romhilt and Estes[14] observed on the basis of a point score system that 62 2% of autopsied hypertrophied hearts met enough electrocardiographic criteria for left ventricular hypertrophy to achieve five points Such criteria were more sensitive from patients with both hypertension and coronary artery disease such a combination was associated with an 88 2% sensitivity compared to 45% with only hypertension and 54 4% with only coronary artery disease A comparison of the point score in our patients with ECG LVH in those with an without hypertension revealed no significant differences Utilizing a point score of 5 or more there were only 3 3% false positive

Why 25% of our patients without hypertension had ECG LVH is uncertain It is possible that some of these patients had clinically unrecognized myocardial infarction and prior undiagnosed hypertension It is well appreciated that in some patients preexisting hypertension may not persist after a myocardial infarction [19, 21] It is also possible that the ECG LVH observed in some of our patients represents a conduction disturbance rather than true myocardial hypertrophy Such a hypothesis is based on the investigations of Piccolo and associates [22] who observed that ECG LVH in some patients was dependent on slowed conduction in the left bundle branch system suggesting that the anatomical hypertrophy may play a less important role Such a mechanism for ECG LVH may well explain the low sensitivity of the electrocardiogram in diagnosing anatomic left ventricular hypertrophy [1, 14] Finally it is well recognized that coronary atherosclerosis per se may be associated with cardiac hypertrophy Pathologic studies [3, 2] have repeatedly demonstrated that myocardial hypertrophy is frequently found with coronary artery disease especially in the setting of preexisting hypertension and congestive heart failure In the pathologic study of Ellis and co workers [2] who excluded cases with hypertension it was observed that cardiomegaly can occur in coronary artery disease even in the absence of congestive heart failure Cardiac hypertrophy was present in 43% of patients with prior myocardial infarction and no history of congestive heart failure In 17% of their cases cardiac hypertrophy was observed even in the absence of a prior myocardial infarction or congestive heart failure indicating as suggested by Mallory and co workers that coronary atherosclerosis by itself may stimulate cardiac hypertrophy Experimental studies in the rat reported by Norman and Coers have demonstrated that ligation of the left descending artery can result in hypertrophy of the left ventricle after 12 weeks Quantitative angiocardiographic studies have demonstrated that ischemic heart disease is commonly associated with increased left ventricular mass Furthermore such studies suggest that the increased left ventricular mass is related to the severity of the coronary artery disease In our study group 47% of patients with ECG LVH had triple vessel disease compared to 32% in the age sex matched controls Pech and co workers[*] speculated that the reparative process after hypoxic necrosis may result in compensatory hypertrophy of the remaining myocardium

Whether or not such changes in the left ventricular myocardium as discussed above can explain ECG LVH in patients with coronary artery disease and no preexisting hypertension is only speculative Interestingly those patients with ECG LVH and no hypertension had a similar Romhilt Estes point score for ECG LVH when compared to patients with hypertension Furthermore a comparison of left ventricular function in these two ECG LVH subgroups revealed no significant differences in the parameters evaluated However the most striking finding was the higher frequency ($p < 0.05$) of main left coronary artery disease in the nonhypertensive ECG LVH group (29%) as compared to the hypertensive ECG LVH group (7%) In a prior report by Cohen and Gorlin [31] the frequency of ECG LVH in patients with main left coronary disease was observed to be 9 6% which is more than twice the frequency (3 9%) we have noted in over 1 000 selected patients with documented ischemic heart disease Furthermore long term follow up of patients with main left coronary artery disease indicated that ECG LVH adversely affects the prognosis [33] It is tempting to speculate that the ominous prognosis associated with ECG LVH may in part be related to the excessive high frequency of main left coronary artery disease observed in this nonhypertensive ECG LVH subgroup

Combining ECG LVH and the presence of left atrial enlargement further defines patients with

Comparison of the inotropic action of digitalis and isoproterenol in younger and older individuals

Dennis V Cokkinos
George D Tsartsalis
Elias T Heimonas
Constantine D Gardikas
Athens Greece

Digitalis and isoproterenol both increase myocardial contractility and are used clinically for the support of the failing myocardium

There has been much discussion about the use of digitalis in the elderly It is well known that older individuals even when they do not present with any definite abnormalities differ functionally from their younger peers[1] Specifically renal function and creatinine clearance deteriorate with age This together with a decrease in muscular mass account for prolongation of digoxin half life and diminution of the volume of distribution which renders older individuals susceptible to digoxin overdosage In many studies[3] increased incidence of digitalis intoxication has been observed in the elderly This however has not been substantiated in more recent prospective studies Some clinicians have discontinued digitalis in elderly persons without documenting any difference in their cardiovascular status Similarly Starr and Luchi could not discern any positive inotropic effect of digitoxin in elderly women using the force ballistocardiogram It is interesting however that no actual clinical study exists in which the inotropic action of digitalis has been compared in younger and older individuals

We undertook to study the action of digitalis in persons younger and older than 60 years of age by the use of systolic time intervals This technique has been employed quite often for the evaluation of the action of digitalis on the myocardium[1] We also employed the same technique to assess the inotropic action of isoproterenol on the cardiac function of older people In a recent study Lakatta and associates[3] found that the myocardium of aged laboratory animals is less sensitive to catecholamines than that of younger ones

From the Professorial Medical Department Evangelismos Hospital, Athens, Greece

Received for publication on Ma 26
Accepted for publication on J 1 4 1

Reprint requests D Cokkinos Dorylaiou Street Athens 601 Greece

Patients and methods

1 *Digitalis study* Two groups of individuals were compared In Group A 10 were male and were female Ages ranged from 15 to 5? years (mean 34 3) In group B (15 males and females) ages ranged from 60 to 76 years (mean 65 3) All individuals in both groups were judged to be free of overt heart disease by clinical electrocardiographic and radiologic evaluation

In both groups the following systolic time intervals (STI) were measured in the basal state and supine position between 8 00 to 10 A M —electromechanical systole (QS 2) left ventricular ejection time (LVET) and pre-ejection period (PEP) the heart rate (HR) corrected indices of these intervals (QS, LVET, PEP were also estimated The PEP/LVET and PEP, LVET, ratios were also calculated The PEP LVET ratio was also corrected for HR according to the regression equations formed by our group and was termed the c(PEP/LVET) ratio According to these equations c(PEP/LVET) = PEP LVET + 0 00168 HR

After the initial study 1 2 mg deslanoside (

0002 8 03/80/120802 + 05$00 .0/0 © 1980 The C V Mosby Co

1 Miller R R Amsterdam E A Bogren H G Massumi R A Zelis, R and Mason D T Electrocardiographic and cineangiograpic correlations in assessment of the location nature and extent of abnormal left ventricular segmental contraction in coronary artery disease Circulation 49 447 1974

2 Saltups A McCallister B D Hallermann F J Wallace R B Smith R E and Frye R L Left ventricular hemodynamics in patients with coronary artery lesions and the electrocardiogram Am J Med 50 8 1971

3 Lee G B Wilson W J Amplatz K and Tuna N Correlation of vectorcardiogram and electrocardiogram with coronary arteriogram Circulation 38 189 1968

4 Martinez Rios M A Da Costa B C B Cecena Seldner F A and Gensini G G Normal electrocardiogram in the presence of severe coronary artery disease Am J Cardiol 25 320 1970

5 Williams R A Cohn P F Vokonas P S Young E Herman M V and Gorlin R Electrocardiographic arteriographic and ventriculographic correlations in transmural myocardial infarction Am J Cardiol 31 595 1973

6. Hilsenrath J., Tabrah, F Hamby R I and Hoffman I Relation of left ventricular contractile patterns in coronary artery disease to the electrocardiogram and vectorcardiogram J Electrocardiography 8 335 1975

7 Hamby R I Hoffman I Hilsenrath J Aintablian A Shanies, S and Padmanabhan V S Clinical hemodynamic and angiographic aspects of inferior and anterior myocardial infarction in patients with angina pectoris Am. J Cardiol 34 513 1974

8 Hamby R I Tabrab F and Gupta M Intraventricular conduction disturbances and coronary artery disease Am. J Cardiol 32 758 1973

9 Kannel W B Doyle J T McNamara P M Quickenton P., and Gordon T Precursors of sudden coronary death Factors related to the incidence of sudden death Circulation 51 606 1975

10 Chiang B N Perlman L V Fulton M Ostrander L D Jr and Epstein F H Predisposing factors in sudden cardiac death in Tecumseh Michigan A prospective study Circulation 41 31 970

11 Kannel, W B Gordan T., Castelli, W P and Mar olis J R Electrocardiographic left ventricular hypertrophy and risk of coronary heart disease The Framingham study Ann Intern Med 72 813 1970

12. Massie E and Walsh T J Clinical vectorcardiography and electrocardiography Chicago 1970 Year Book Medical Publishers Inc., pp 129 231 232

13 Morris J J Estes E H Whalen R E Thompson H K McIntosh, H D P wave analysis in valvular heart disease Circulation 29 242 1964

14 Romhilt D W and Estes E H A point score system for the ECG diagnosis of left ventricular hypertrophy AM HEART J 75 752 1968

15 Hamby R I Angina pectoris A clinical-electrocardiographic angiographic correlative study in 510 patients *in* Cardiovascular clinics Brest A N ed Philadelphia 1977 F A. Davis Company pages 70-109

16. Bruschke A. V G The diagnostic significant of the coronary arteriogram A study of its value in relation to other diagnostic methods, Utrecht 1970 Kemink en Zoon N V

17 Baston, H C An Introduction to statistics in the medical sciences, G Burgess Publishing Co Minneapolis 1963

18 Olson, H G., Lyons, K. P Aronow W S Kuperus, J Orlando J and Huges D Prognostic value of a persistently positive technetium 99m stannous pyrophosphate myocardial scintigram after myocardial infarction Am J Cardiol 43 889 1979

19 Master A M Jaffe H L Dack S and Silver N The course of the blood pressure before during and after coronary occlusion AM HEART J 29 9? 1943

20 Palmer J H and McGill M D The blood pressure in the years following recovery from coronary thrombosis, Lancet 1 741 1937

21 Chambers W N Blood pressure studies in 100 cases of coronary occlusion with myocardial infarction Am J Med Sci 213 40 1947

22. Piccolo E Raviele A Delise P., Dainese F., Pascotto P Totaro G Sartori F and D Este D The role of left ventricular conduction in the electrogenesis of left ventricular hypertrophy An electrophysiologic study in man Circulation 59 1044 1979

23 Bean W B Infarction of the heart II Clinical course and morphologic findings Ann Intern Med 12 71 1938

24 Clawson B J Coronary sclerosis An analysis of nine hundred and twenty-eight cases AM HEART J 17 387 1939

25 Connolly E F and Littman D Coronary arteriosclerosis and myocardial hypertrophy N Engl J Med 245 753 1957

26 Ellis L B Allison R B., Rodriguex F L. and Robbins S L. Relation of the degree of coronary artery disease and of myocardial infarctions to cardiac hypertrophy and chronic congestive heart failure N Engl J Med 266 525 1962

27 Mallory G K White P D and Salcedo Salgar J The speed of healing of myocardial infarction A study of the pathologic anatomy in seventy two cases AM HEART J 18 647 1939

28 Norman T D and Coers C R Cardiac hypertrophy after coronary artery ligation in rats Arch Pathol 69 181 1960

29 Pech H J Witte J Romaniuk R Parsi R A and Porstmann W Left ventricular mass in coronary artery disease without hypertension Haemodynamic and angiographic study Br Heart J 36 363 1974

30 Hamilton G W Murray J A and Kennedy J W Quantitative angiocardiography in ischemic heart disease The spectrum of abnormal left ventricular function and the role of abnormally contracting segments Circulation 45 1065 1972

31 Moraski R E Russell R O Jr Smith M and Rackley C E Left ventricular function in patients with and without myocardial infarction and one two or three vessel coronary artery disease Am J Cardiol 35 1 19 5

32 Rackley C E Dear H D Baxley W A Jones, W B and Dodge H T Left ventricular chamber volume mass and function in severe coronary artery disease Circulation 41 605 1970

33. Cohen M V and Gorlin R Main left coronary artery disease Clinical experience from 1964 1974 Circulation 52 275 1975

34 Lim J S Proudfit W L and Sones F M. Left main coronary arterial obstruction Long term follow up of 141 nonsurgical cases Am J Cardiol. 36 131 1975

35 Rios, J C Schatz J., and Heeshel J C P wave analysis in coronary artery disease Chest 66 146 1974

36 Rios, J C Sinderson T., and Goldberg S Electrocardiographic angiographic correlations in coronary heart disease from Clinical electrocardiographic correlations, *in* Brest A N and Rios, J C eds Cardiovascular clinics Philadelphia 1977 F A Davis Co pp 111 125

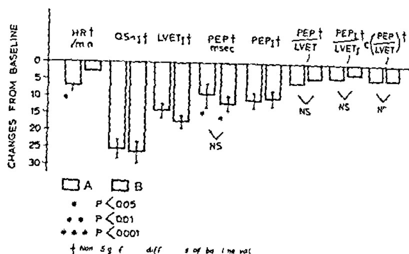


Fig 1 Changes in systolic time intervals after the administration of deslanoside C 1.2 mg intra ve sly A Group A B Group B Changes from the baseline are expressed in the ordinate

Table II Influence of isoproterenol infusion (2 μg/minute × 5 minutes) on systolic time interval

	HR/ min	QS (msec)	QS_I	LVET (msec)	$LVET_I$	PEP (msec)	PEP_I	PEP/ LVET	PEP/ LVET	C(PEP/ LVET
1 Before isoproterenol										
Group A	83 3 ± 2 7	370 2 ± 8 8	539 5 ± 5 7	267 4 ± 6.2	402 3 ± 5 1	102 8 ± 5 8	136 1 ± 5 2	0 386 ± 0 0?	0 339 ± 0 015	0.[illegible] 0.025
Group B	65 8 ± 2 9	399 1 ± 4 3	535 7 ± 3 6	301.5 ± 5 8	412 8 ± 3 9	102 3 ± 3 1	123 5 ± 3 9	0.3?? ± 0 014	0 299 ± 0 010	0 0[illegible]
Difference between A and B	−17 5 p < 0 001	+27 9	−3 8	+34 1	+9 9	−0 5	−12 6	−0 064	−0 040	−0.0[illegible]
2 After isoproterenol										
	118 9 ± 6 8	270 9 ± 10 9	511.5 ± 7 1	209 6 ± 8 3	40? 8 ± 6 4	61 3 ± 4 8	108 9 ± 3 8	0.294 ± 0 0?4	0 2 1 ± 0 011	0.?? 0.0??
	91 0 ± ? 7	293 9 ± 4	486 0 ± 7 2	224 9 ± 7 9	380 2 ± 7 1	68 9 ± 3 7	105 7 ± 4 0	0 312 ± 0 0?1	0 ?73 ± 0 012	0.15? +0.0??
	−27 0	+23 0	−25.?	+15 3	−22 4	+7 6	−3 2	+0 018	+0 008	+0.01?

HR/ min	QS	LVET	PEP (msec)	PEP	PEP/ LVET	PEP_I/ $LVET_I$	C(PEP/ LVET)
Difference between 1 and 2							
+3? 6 ± 5 ? P < 0 001 + 4? ?	−29 0 ± 6 1 < 0 001	−0 1 ± 4 3	−41 5 ± 4 1 < 0 001	−?7 2 ± 3 9 < 0 001	−0.09? ± 0 012 < 0 001 −23 8?	−0 065 ± 0 009 < 0 001 −20 0?	−0.1?? 0? 5 < 0? −6 ?
+26 1 +2.9 P < 0 001 +39 7?	−43 8 ± ?9 < 0 001	−32 5 ± 6 1 < 0 001	−33 4 ± 4 5 < 0 001	−17 8 ± 3 9 < 0 001	−0 010 ± 0 0?1 −3 1?	−0 0?0 ± 0 01? −6 6?	−0.0?4 +0.0?? < 0.0? −23.?
−9 5	−20 8	+32 6	+8 1	+9 4	+0 08? < 0 001	+0 045 < 0 01	+0.0?? < 0 ?1

HR heart rate I isoproterenol ± S E M
Only significant differences designated

Table I Influence of deslanoside C (1.2 mg) on systolic time intervals

	HR/ min	*QS (msec)*	*QS*	*LVET (msec)*	*LVET*	*PEP (msec)*	*PEP*	*PEP/ LVET$_I$*	*PEP/ LVET*	*c(PEP/ LVET)*
1 Before deslanoside										
Group A	77.6	393.6	55[illegible].7	287.7	406.7	114.9	145.9	0.416	0.359	0.283
	± 2.6	± 7.3	± 5.5	± 5.0	± 4.0	± 3.9	± 4.[illegible]	± 0.031	± 0.009	± 0.015
Group B	72.5	389.9	540.6	273.2	394.9	116.6	145.6	0.431	0.369	0.310
	± 2.[illegible]	± 5.6	± 3.4	± 5.8	± 4.1	± 3.4	± 2.5	± 0.018	± 0.012	± 0.017
Difference between A and B	−5.1	−3.7	−12.1	−14.5	−11.8	+1.7	−0.3	+0.015	+0.010	+0.027
2 After deslanoside										
	70.4	382.8	5[illegible]7.2	2[illegible]6.[illegible]	39[illegible].5	106.5	134.7	0.388	0.343	0.270
	± 3.0	± 7.5	± 5.3	± 6.[illegible]	± 3.9	± [illegible].9	± 2.9	± 0.012	± 0.008	± 0.011
	69.5	369.5	514.1	262.0	3[illegible].4	102.8	135.0	0.412	0.358	0.297
	± [illegible].6	± 6.5	± 4.2	± 6.5	± 10.2	± [illegible].6	± 3.1	± 0.017	± 0.011	± 0.017
	−0.9	−13.3	−13.1	−14.[illegible]	−1[illegible].1	−3.7	+0.3	+0.024	+0.015	+0.0[illegible]7

HR/ (min)	*QS*	*LVET*	*PEP (msec)*	*PEP*	*PEP/ LVET*	*PEP/ LVET*	*c(PEP/ LVET)*
Difference between 1 and 2							
−7.2	−[illegible]5.5	−14.2	−8.4	−11.2	−0.0[illegible]5	−0.015	−0.013
±1.7	±[illegible].9	±2.4	±3.[illegible]	±[illegible].3	±0.009	± 0.006	±0.009
<0.001	<0.001	<0.001	<0.01	<0.001		<0.05	
−9.2%					−5.9%	−4.2%	−4.6%
−3.0	−26.4	−17.5	−13.8	−10.6	−0.019	−0.011	−0.013
±1.1	± 3.1	±2.0	±2.[illegible]	±[illegible].3	±0.010	±0.07	±0.010
<0.05	<0.001	<0.001	<0.001	<0.001			
−4.3%					−4.4%	−3.0%	−4.[illegible]%
+4.2	0.9	−3.3	−5.4	+0.6	+0.006	+0.004	0

HR heart r te D desl nos de C ± S.E.M
Only signific t d ff rences ar des gn ted

was given intravenously to all individuals and the STI were measured 60 minutes later. By this time this drug has reached a peak effect.

2 Isoproterenol study

Group A. In 15 individuals (four males, 11 females) aged 22 to 42 years (mean 33.3) an intravenous infusion of 5% glucose was started. 30 minutes later the STI were calculated and isoproterenol was infused at a rate of 2 μg/minute for 5 minutes.[11] Thirty seconds after the end of the infusion STI were measured again.

Group B comprised 15 individuals (14 males, one female) aged 60 to 75 years (mean 67.7). The same procedure as in Group A was followed.

The differences in HR, QS$_I$, LVET$_I$, PEP, PEP$_I$, PEP/LVET, PEP$_I$/LVET$_I$ and c(PEP/LVET) before and after deslanoside or isoproterenol were compared by the paired t test. We included PEP in both its rate corrected and uncorrected forms because in contrast to QS or LVET it does not appreciably change with HR alterations.

Results

1 Digitalis study (Table I)

a. Before administration of the drug there was no difference in heart rate or systolic time intervals between Groups A and B.

b. In both groups after deslanoside a decrease in HR was observed together with shortening of the QS$_I$, LVET$_I$, PEP and PEP$_I$. The PEP/LVET, PEP$_I$/LVET$_I$ and c(PEP/LVET) ratios did not change appreciably.

The changes seen with deslanoside administra

LVET did not significantly change Thus our observations probably represent a real difference and correspond to the differences found in animals[14] We do not know whether any practical significance could be ascribed to this finding However it is possible that the therapeutic value of catecholamines is narrower in older than in younger individuals since the increases in oxygen requirements produced by these agents are not accompanied by a concomitant increase in stroke volume

Groups A and B of the isoproterenol study were not completely comparable Group B comprised more men than women while the opposite was true of Group A Perhaps the difference in base line heart frequency can be attributed not only to age which is associated with a decrease in heart rate but to sex as well women usually manifesting higher heart rates than men Still if this difference in any way can be ascribed to greater sympathetic activity in Group A this should render our results even more significant as isoproterenol would be expected to exert a smaller influence in Group A

Summary

The positive inotropic effects of digitalis (deslanoside C 1 2 mg intravenously) and isoproterenol (2 μg/minute intravenously) were compared in two groups of younger and older individuals using the systolic time interval method

Both groups responded in a completely comparable way to deslanoside C However after isoproterenol administration the LVET of the older group was significantly shortened Consequently the PEP/LVET ratio did not change significantly This difference is attributed to a lesser increase of the stroke volume in the older group

REFERENCES

1 Burch, G E Interesting aspects of geriatric cardiology Am Heart J 89 99 1975
2. Ewy G A Kapadia G G and Yao L Digoxin metabolism in the elderly Circulation 39 449 1969
3 Hurwitz N and Wade O L Intensive hospital monitoring of adverse reactions to drugs, Br Med J 1 … 1969
4 Soffer A. The changing clinical picture of d… intoxication Arch. Intern Med 107 681 1961
5 Storstein O Hansteen V Hatle L. Hillestad, L … Storstein L. Studies on digitalis Am Heart J 93 … 1977
6 Dall J L C Digitalis intoxication in elderly pa… Lancet 1 194 1965
7 MacDonald Hull S and Mackintosh A Discontinua… tion of maintenance digoxin therapy in general practi… Lancet 2 1054 1977
8 Starr I and Luchi R J Blind study on the action of digitoxin on elderly women, Am Heart J 78 … 1969
9 Weissler A M and Schoenfeld C D Effect of digitalis on systolic time interval in heart failure Am. J Med Sc 259 4 1970
10 Carliner N H Gilbert C A Pruitt A. N and Goldberg L. I Effects of maintenance digoxin therapy on systolic time intervals and serum digoxin concentrations Circulation 50 94 1974
11 Hoeschen R J and Cuddy T E Dose response relation between therapeutic levels of serum digoxin and systolic time intervals, Am J Cardiol 35 469 1975
12 Cokkinos D V., Demopoulos J N Heimonas, E T … Vorides E M Influence of digitalis on cardiac function before and after autonomic blockade Acta Cardiologica 33 185 1978
13 Lakatta E G Gestenblith G Angelic Shock, N W and Weisfeldt M L Diminished inotropic response of aged myocardium to catecholamines, Circ Res. 36 … 1975
14 Weissler A M Harris W S and Schoenfeld, C D Bedside technics for the evaluation of ventricular function in man Am J Cardiol 23 577 1969
15 Cokkinos, D., Heimonas E Demopoulos, J and Gerbicas C D The influence of heart rate increase on the uncorrected pre-ejection period/left ventricular ejection time ratio in normal individuals Br Heart J 38 9 … 1976
16 Forester W Lewis R P Weissler A M and Wilke T A The onset and magnitude of the contractile response to commonly used digitalis glycosides in normal subjects Circulation 49 517 1974
17 Boudoulas H., Lewis R P., Kates, R E and Dalamangas G Hypersensitivity to adrenergic stimulation after propranolol withdrawal in normal subjects, Ann Intern Med 87 443 1977
18 Burch G E Elegant digitalization for congestive heart failure Am Heart J 83 543 1972
19 Guarnieri T Spurgeon H A Weisfeldt, M L, and Lakatta E G Unaltered toxicity but decreased inotropic response to acetylstrophanthidin in senescence (Abstr) Circulation 58 II 147 1978
20 Lewis R P Rittgers S E Forrester W F and Boudoulas H A critical review of the systolic time intervals Circulation 56 146 1977

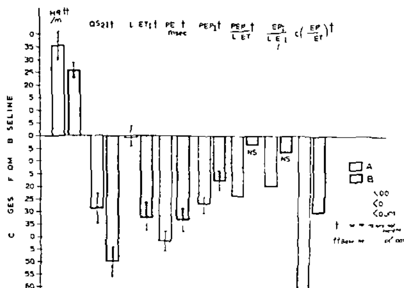


Fig 2 Changes in systolic time interval after the adm ni tration of i proterenol, 2 0 / ,/minute intravenou ly for 5 minutes Changes from the ba eline are expressed in the ordinate

ion were quite similar in the two groups (Fig 1)

2 Isoproterenol study (Table II)

a Before administration of the drug HR was significantly higher in Group A ($p < 0.001$ Fig 2)

b After isoproterenol the HR increase was similar in both groups QS , PEP and PEP, also were equally shortened The LVET, did not change significantly in Group A but was significantly shortened in Group B ($p < 0.001$) The PEP/LVET and PEP,/LVET, ratios decreased significantly only in Group A The c(PEP/LVET) *ratio diminished at the* $p < 0.001$ *level in* Group A but only at the $p < 0.05$ level in Group B Moreover the percent diminution of all three ratios was significantly greater in Group A Fig 2)

Discussion

From our results it can be seen that digitalis exerts comparable *inotropic effects on the myo*cardium of younger and older individuals Our findings are similar to those of previous authors Thus Weissler and Schoenfeld found that decreases in QS , and PEP, were more significant that LVET, Carliner and associates found significant changes of QS , PEP PEP, and PEP/LVET with maintenance digoxin while Hoeschen and Cuddy found changes in QS and LVET only but not in PEP or PEP/LVET In patients with transvenous pacemakers in whom rate correction was not necessary we found a significant decrease in QS and PEP only The conclusion of most authors is that QS , is the most sensitive index *of digitalis action on systolic time intervals* followed by PEP while LVET and PEP/LVET changes are variable Thus although we did not try elegant digitalization we can say that *digitalis has a definite place in the treatment of* cardiac failure in the elderly Of course provision must be made for the greater susceptibility of older individuals for toxic accumulation of the *drug We did not measure drug levels in the* serum an assay difficult with deslanoside C but the dose we employed is one used quite often clinically Our findings are at variance with those *very recently* reported by Guarnieri and colleagues who found that the heart of aged rats was less sensitive to ouabain than that of younger ones However the conditions of the two studies were completely different

We are intrigued by our results with isoproterenol It is postulated that catecholamines affect the LVET in two diverse directions—the contraction time is abbreviated thus the LVET tends to shorten while the stroke volume is augmented tending to prolong the ejection time We assume that in the aged individuals the stroke volume did not increase appreciably subsequently the PEP/

LVET did not significantly change Thus our observations probably represent a real difference and correspond to the differences found in animals[13] We do not know whether any practical significance could be ascribed to this finding However it is possible that the therapeutic value of catecholamines is narrower in older than in younger individuals since the increases in oxygen requirements produced by these agents are not accompanied by a concomitant increase in stroke volume

Groups A and B of the isoproterenol study were not completely comparable Group B comprised more men than women while the opposite was true of Group A Perhaps the difference in base line heart frequency can be attributed not only to age which is associated with a decrease in heart rate but to sex as well women usually manifesting higher heart rates than men Still if this difference in any way can be ascribed to greater sympathetic activity in Group A this should render our results even more significant as isoproterenol would be expected to exert a smaller influence in Group A

Summary

The positive inotropic effects of digitalis (deslanoside C 1 2 mg intravenously) and isoproterenol (2 μg/minute intravenously) were compared in two groups of younger and older individuals using the systolic time interval method

Both groups responded in a completely comparable way to deslanoside C However after isoproterenol administration the LVET of the older group was significantly shortened Consequently the PEP/LVET ratio did not change significantly This difference is attributed to a lesser increase of the stroke volume in the older group

REFERENCES

1 Burch G E Interesting aspects of geriatric cardiology AM HEART J 89 99 1975
2 Ewy G A Kapadia G G and Vao L Digoxin metabolism in the elderly Circulation 39 449 1969
3 Hurwitz N and Wade O L Intensive hospital ... toring of adverse reactions to drugs, Br Med J 1 ... 1969
4 Soffer A The changing clinical picture of digi... intoxication Arch Intern Med. 107 681 1961
5 Storstein O Hansteen V Hatle L., Hillestad, L ... Storstein L Studies on digitalis AM. HEART J 93 ... 1977
6 Dall, J L C Digitalis intoxication in elderly pa... Lancet 1 194 1965
7 MacDonald Hull S and Mackintosh, A Disconti... tion of maintenance digoxin therapy in general pr... Lancet 2 1054 1977
8 Starr I and Luchi R J Blind study on the ac... digitoxin on elderly women AM HEART J 78 ... 1969
9 Weissler A M and Schoenfeld C D Effect of digi... on systolic time interval in heart failure Am J Med ... 259 4 1970
10 Carliner N H., Gilbert C A., Pruitt A. N and G... berg L. I Effects of maintenance digoxin thera... systolic time intervals and serum digoxin concentra... Circulation 50 94 1974
11 Hoeschen R J and Cuddy T E Dose-response ... tion between therapeutic levels of serum digoxin ... systolic time intervals, Am J Cardiol. 35 469 1975
12 Cokkinos D V Demopoulos, J N Heimonas, E.T ... Vorides E M Influence of digitalis on cardiac func... before and after autonomic blockade Acta Cardiol ... 33 185 1978
13 Lakatta E G., Gestenblith G Angelic Shock, ... and Weisfeldt, M L. Diminished inotropic respons... aged myocardium to catecholamines, Circ. Res. 36 ... 1975
14 Weissler A. M Harris W S and Schoenfeld, C. ... Bedside technics for the evaluation of ventricular ... tion in man Am J Cardiol 23 577 1969
15 Cokkinos D Heimonas E Demopoulos, J and G... cas C D The influence of heart rate increase ... uncorrected pre-ejection period/left ventricular ej... time ratio in normal individuals Br Heart J 38 ... 1976
16 Forester W Lewis R P Weissler A. M and W... A The onset and magnitude of the contractile res... to commonly used digitalis glycosides in normal sub... Circulation 49 517 1974
17 Boudoulas H Lewis R P Kates, R E and Dal... gas G Hypersensitivity to adrenergic stimulation ... propranolol withdrawal in normal subjects, Ann. In... Med 87 443 1977
18 Burch, G E Elegant digitalization for congestive ... failure AM HEART J 83 543 1972
19 Guarnieri T., Spurgeon H A. Weisfeldt M. L ... Lakatta E G Unaltered toxicity but decreased in... ic response to acetylstrophanthidin in sene... (Abstr) Circulation 58 II 147 1978
20 Lewis R P Rittgers S E Forrester W F ... Boudoulas H A critical review of the systolic ... intervals Circulation 56 146 1977

The M mode echocardiogram in Fabry s disease

John L. Bass M D
Savitri Shrivastava M D D M
Gregory A Grabowski M D *
Robert J Desnick M D Ph D **
James H Moller M D
Minneapolis Minn

abry s disease an inherited glycosphingolipid torage disease results from the defective activity f the lysosomal hydrolase alpha galactosid se A The major glycosphingolipid substrate rihexosyl ceramide accumulates in plasma and he lysosomes of the kidneys heart and vasculai ndothelium [1] The major clinical manifestations of this sex linked disease—angiokeratoma acro paresthesias myocardial and cerebral infarction and renal failure—result from progressive sub trate deposition in endothelial cells and eventual occlusion of small arterioles Deposition of tri exosyl ceramide in the myocardium and cardiac conduction system can lead to thickening of ventricular walls and arrhythmias [4] Abnormali ies of the mitral and aortic valve leaflets have also been described Findings from the physical examination electrocardiogram and chest roent genogram may not indicate the full extent of cardiac involvement The sensitive detection of uch involvement may be of prognostic value in evaluation of these patients

Since echocardiography may provide a means to assess noninvasively the presence and natural history of cardiac involvement in patients with Fabry s disease a prospective echocardiographic study was undertaken in hemizygous affected males and heterozygous carrier females of this X linked disease Echocardiographic findings of patients with Fabry s disease have not been pre viously described

From the Department of Pediatrics University of Minnesota Hosp tals, Minneapolis Minn

This study was supported in part by the Dwan Family Fund Minne p lis by Grant HL0 359-01A1 from the National Heart Lung and Blood Institute National Institutes of Health Bethesda Md and by Grant RR400 from the General Clinical Research Center Program of the Division of Research Resources, Bethesda Md

Received for publication Aug 10 1979

Accepted for publication Jan 10 1980

Reprint requests John L. Bass, M D Box 94 Mayo Memorial Bldg University of Minnesota Hospitals Minneapolis, Minn 55455

*Recipient of Post Doctoral Fellowship 1F32 HD05408 from the National Institutes of Health Bethesda Md

**Recipient of Career Department Award K04 AM 004 from the National Institutes of Health Bethesda Md

Materials and methods

Thirty two patients with Fabry s disease 25 hemizygotes and seven heterozygotes seen at the University of Minnesota form the basis of this report Each hemizygote had typical clinical find ings of Fabry s disease and was shown to lack detectible levels of alpha galactosidase A in plas ma leukocytes and/or fibroblasts Heterozygotes had intermediate alpha galactosidase A levels and/or elevated urinary trihexosyl ceramide lev els The patients were examined for evidence of cardiac disease or hypertension

Echocardiograms were performed with the transducer in the third or fourth intercostal space near the left sternal border and perpendicular to the chest wall while recording the mitral valve anterior leaflet Recordings were made on a Smith Kline Instruments ultrasonoscope inter faced with a strip chart recorder The echocardio grams were measured with calipers where the technical quality of the recording was adequate for evaluation End diastolic measurements were made at the time of the onset of the QRS complex End systolic measurements were made at the time of aortic valve closure or maximal excursion of the left ventricular posterior wall Measurements were made utilizing leading edge

0002 8 03/80/120807 + 06800 60/0 © 1980 The C V Mosby Co

EFERENCES

Wilson J R., and Lampman J Heparin therapy A randomized prospective study Am Heart J 97 155 1979

Mant M J Thong K L Birtwhistle R V et al Haemorrhagic complications of heparin therapy Lancet 1 1133 1977

Salzman F W., Deykin D Shapiro R M and Rosenbert R Management of heparin therapy N Engl J Med 292 1046 1975

Glazier R L and Crowell F R Randomized prospective trial of continuous vs intermittent heparin therapy J A M A 236 1365 1976

Sasahara A A. Therapy for pulmonary embolism J A M A 229 1795 1974

Moser K M, State of the art Pulmonary embolism Am Rev Resp Dis 115 829 1977

Red Book 1979 Oradell N J 1979 Medical Economics Co page 227

Hospital Price List and Ordering Information Effective February 1 1979 Travenol Laboratories Inc One Baxter Parkway Deerfield Illinois 60015

Wessler S Venous thromboembolism Scope of the problem *in* Prophylactic Therapy of Deep Vein Thrombosis and Pulmonary Embolism Frantantoni J and Wessler S coeditors Washington D C 1975 DHEW Publication No (NIH) 76 866 p 1

Coon W W Willis P W III and Keller J B Venous thromboembolism and other venous disease in the Tecumseh Community Health Study Circulation 48 839 1973

11 Rosenblum D Bleeding and clotting disorders and anticoagulation *in* Manual of Medical Therapeutics Boedeker E C., and Dauber J H eds Boston 1974 21st edition Little Brown and Company p 309

Reply

To the Editor

Doctors Self and Vanderbush have shown that equipment and labor inputs for the *intermittent method of heparin administration* may be quite a bit less than for the continuous method This is an undeniably pertinent fact bearing on the choice of a preferred method

Our study suggested that neither method had a clear advantage in reducing risk of serious hemorrhage The small numbers of patients in this study limits the certainty with which this conclusion is justified Nevertheless, until convincing evidence of less efficacy or greater risk is presented we would agree that it is quite reasonable to recommend the intermittent method on the basis of economic considerations

James H Lampman MD
John R Wilson MD
Cuyahoga County Hospital
3395 Scranton Rd
Cleveland Ohio 44109

he M-mode echocardiogram in Fabry s disease

ohn L Bass M D
savitri Shrivastava M D D M
Gregory A Grabowski M D *
Robert J Desnick M D Ph D **
ames H Moller M D
Minneapolis Minn

abry s disease an inherited glycosphingolipid torage disease results from the defective activity f the lysosomal hydrolase alpha galactosid se A[1] The major glycosphingolipid substrate rihexosyl ceramide accumulates in plasma and he lysosomes of the kidneys heart and vasculai ndothelium [1] The major clinical manifestations f this sex linked disease—angiokeratoma acro aresthesias myocardial and cerebral infarction and renal failure—result from progressive sub trate deposition in endothelial cells and eventual cclusion of small arterioles Deposition of tri exosyl ceramide in the myocardium and cardiac onduction system can lead to thickening of entricular walls and arrhythmias Abnormali ies of the mitral and aortic valve leaflets have lso been described [4] Findings from the physical xamination electrocardiogram and chest roent enogram may not indicate the full extent of ardiac involvement The sensitive detection of uch involvement may be of prognostic value in valuation of these patients

Since echocardiography may provide a means to assess noninvasively the presence and natural history of cardiac involvement in patients with Fabry s disease a prospective echocardiographic tudy was undertaken in hemizygous affected males and heterozygous carrier females of this X linked disease Echocardiographic findings of patients with Fabry s disease have not been pre viously described

Materials and methods

Thirty two patients with Fabry s disease 25 hemizygotes and seven heterozygotes seen at the University of Minnesota form the basis of this report Each hemizygote had typical clinical find ings of Fabry s disease and was shown to lack detectible levels of alpha galactosidase A in plas ma leukocytes and/or fibroblasts Heterozygotes had intermediate alpha galactosidase A levels and/or elevated urinary trihexosyl ceramide lev els The patients were examined for evidence of cardiac disease or hypertension

Echocardiograms were performed with the transducer in the third or fourth intercostal space near the left sternal border and perpendicular to the chest wall while recording the mitral valve anterior leaflet Recordings were made on a Smith Kline Instruments ultrasonoscope inter faced with a strip chart recorder The echocardio grams were measured with calipers where the technical quality of the recording was adequate for evaluation End diastolic measurements were made at the time of the onset of the QRS complex End systolic measurements were made at the time of aortic valve closure or maximal excursion of the left ventricular posterior wall Measurements were made utilizing leading edge

From th Dep rtment of Ped tri s University of Minnesot Hosp als Minn polis, Minn

This st dy was supported in part by the Dwan Family Fund Minne p lis, by Grant HL0 359-01A1 from the N tional H art Lung a d Blood Inst tute Nat onal Inst tutes of H lth Bethesd Md d by Grant RR400 from the Gener l Cl n cal Research Cent s Prog m of he Di ision of Research Resources, B thesda Md

Recei ed f r publi ti n Aug 10 19 9

Accepted fo publi ati n J n 10 1980

Reprint requests John L. Bass, M D Box 94 Mayo Memorial Bld Un rsity of M nnesota Hospit ls Minne polis, Minn 5o4 5

*Recip nt f Post Doct ral Fellow hip 1F3 HD05408 from the Nati n l Inst tutes f He lth, Bethesd Md

**Recip nt of Ca eer Departm nt Aw rd K04 AM 004 fr m th Nati nal Institutes f He lth Bethesda Md

00 -8 03/80/1?0807 + 06?00 60/0 © 1980 The C V Mosby Co

Table I

Case no	Age (yrs)	Body surface area (m²)	Diastolic IVS thickness (mm)	Diastolic LVPW thickness (mm)	IVS/LVPW ratio	IVS motion	Left ventricular dimension: Systole (mm)	Left ventricular dimension: Diastole (mm)	Shortening fraction	Aortic root dimension (mm)	Left atrial dimension (mm)
Hemizygotes											
1	16	1.5	7	6	1.2	Nl	30	47	0.36	30	[illegible]
2	17	1.3	9	6	1.5	Nl	34	51	0.33	33	33
3	18	1.6	10	10	1.0	Nl	32	45	0.?9	29	29
4	18	1.3	10	7	1.4	Nl	28	47	0.40	30	[illegible]
5	20	1.8	12	9	1.3	Nl	31	50	0.38	33	[illegible]
6	21	1.8	13	16	0.7	Nl	30	48	0.38	34	[illegible]
7	22	1.6	10	8	1.2	Nl	36	54	0.33	3?	30
8	23	1.8	10	9	1.1	Nl	34	46	0.?6	40	34
9	25	1.4	10	13	0.8	Nl	31	43	0.28	38	[illegible]
10	27	1.9	CE	CE	CE	CE	CE	CE	CE	?8	[illegible]
11	27	2.2	13	13	1.0	Nl	33	50	0.34	41	25
12	29	2.3	12	9	1.3	Nl	39	51	0.?4	4?	39
13	33	2.5	15	22	0.8	Nl	54	?2	0.25	41	[illegible]
14	34	2.0	17	13	1.3	Flat	25	40	0.38	35	[illegible]
15	35	2.0	15	12	1.2	Flat	31	47	0.34	4?	[illegible]
16	36	1.8	16	13	1.2	Nl	23	48	0.31	[illegible]	33
17	37	1.8	14	11	1.3	Flat	45	66	0.3?	41	[illegible]
18	38	1.7	10	12	0.8	B	CE	4?	CE	39	29
19	39	1.7	9	9	1.0	Nl	29	51	0.43	35	36
20	39	1.8	15	14	1.1	Flat	27	46	0.41	40	32
21	43	1.8	17	16	1.1	Nl	34	50	0.32	46	[illegible]
22	44	1.8	11	10	1.1	B	CE	4?	CE	31	37
23	44	1.4	18	14	1.3	Flat	31	4?	0.26	41	[illegible]
24	53	1.6	10	13	0.8	Flat	35	53	0.34	4?	30
25	54	2.1	?5	19	1.3	Nl	23	40	0.43	38	[illegible]
Heterozygotes											
1	15	1.4	10	11	0.9	Nl	25	39	0.36	30	[illegible]
2	19	1.8	10	7	1.4	Nl	30	47	0.36	3?	[illegible]
3	28	1.8	7	7	1.0	Nl	30	41	0.?6	28	[illegible]
4	41	1.6	11	9	1.2	Nl	27	41	0.34	CE	CE
5	41	1.5	CE	11	CE	CE	CE	CE	CE	30	[illegible]
6†	45	1.4	18	13	1.4	Flat	25	45	0.44	30	[illegible]
7	59	2.0	11	13	0.9	Nl	31	48	0.35	31	3

Abbreviations B = type B paradoxical ventricular septal motion BSA = body surface area CE = could not evaluate IVS = interventricular septum LVPW = left ventricular posterior wall Nl = normal [illegible] = hypertensive

† = full expression in heterozygote

dimension of our 11 patients in this same age range (50.5 mm) was not statistically different. The diastolic left ventricular dimension was measured in six heterozygotes with a mean of 43.5 mm.

The left ventricular shortening fraction was calculated in 22 hemizygous patients. The nine patients under 26 years had a shortening fraction of 0.33 ± 0.05 (mean ± standard error of the mean), not significantly different from the 13 older patients (0.33 ± 0.02 mean ± standard error of the mean). Nor was this different from the mean value of 0.34 found by Gertsenblith and associates in 37 normal adults between 25 and [illegible] years of age. Shortening fraction was calculated in six heterozygotes with a mean of 0.35.

The ratio of diastolic ventricular septal thickness to left ventricular posterior wall thickness was greater than 1.3 in two of the 21 normotensive hemizygotes and in two of six heterozygotes. However three of these four patients had a ventricular septal thickness of 10 mm or less. Only the clinically affected heterozygote had an abnormally thick ventricular septum with a ra[illegible]

sent in one hemizygote who also had an apical late systolic murmur Another patient with auscultatory evidence of aortic regurgitation showed diastolic flutter of the mitral valve leaflets Eccentric closure of the aortic valve was recorded in three hemizygotes who also had increased aortic root dimensions

The aortic root dimension was measured in each hemizygote In the nine patients less than 26 years of age the aortic root dimension was 33 2 ± 1.2 mm (mean ± standard error of the mean) and in two (22%) it was greater than 37 mm (the maximum reported by Feigenbaum in normal adults) In the 16 hemizygotes older than 26 years the aortic root dimension was 38 1 ± 1 2 mm (mean ± standard error of the mean see Fig 2) and 12 (75%) showed a dimension greater than 37 mm This difference in aortic root dimensions between the age groups was statistically significant ($p < 0.01$) Gertsenblith and associates found a mean aortic root diameter of 30 9 mm in 45 adults between 25 and 44 years of age The mean aortic root dimension of our 15 hemizygous patients between 25 and 44 years was 38 6 mm a statistically significant difference from normal ($p < 0.001$) When the aortic root dimension was compared to body surface area as a root function the correlation ($R = 0.34$) was not statistically significant ($p > 0.05$)

The echocardiographic aortic root dimension was measured in six of the heterozygotes and was less than 37 mm in each

The diastolic left ventricular posterior wall thickness was measured from the echocardiograms of 21 normotensive hemizygous patients In the patients under 26 years of age the left ventricular posterior wall thickness (9 6 ± 1 3 mm mean ± standard error of the mean) was not significantly different ($p > 0.05$) from the 12 patients older than 26 years (12 4 ± 0 7 mm mean ± standard error of the mean see Fig 3) Whereas two of the nine younger patients (22%) had a diastolic left ventricular posterior wall thickness greater than 11 mm (the maximum thickness reported by Feigenbaum in normal individuals) eight of the 12 older patients (67%) had a measurement greater than 11 mm Gertsenblith and associates[7] reported the echocardiographic diastolic left ventricular wall thickness in 33 adults between 25 and 44 years of age and found a mean of 8 7 mm The mean thickness in our 12 normotensive hemizygotes in this same age

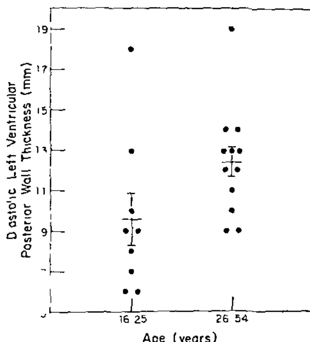


Fig 3 Distribution of echocardiographic left ventricular wall thickness in patients with Fabry's disease *Lines and intervals* indicate mean ± one standard error of the mean *The stippled area* indicates the expected range of normal from Feigenbaum

range was 11 9 mm a statistically significant difference ($p < 0.001$) When the left ventricular posterior wall thickness was compared to body surface area as a linear function the correlation ($R = 0.42$) was not statistically significant ($p > 0.05$) The echocardiographic diastolic left ventricular posterior wall thickness was measured in each heterozygote and was greater than 11 mm in two of the seven

Systolic and diastolic left ventricular internal dimensions were measured from the echocardiograms of 22 hemizygous patients Of the three patients in whom these measurements were not made two were excluded because of paradoxical ventricular septal motion and the third was excluded because the quality of the echocardiogram was technically inadequate The diastolic left ventricular dimension in the nine patients under 26 years (47 8 ± 1 11 mm mean ± standard error of the mean) was not significantly different from the 13 patients over 26 years of age (50 5 ± 2 58 mm mean ± standard error of the mean) Gertsenblith and associates found a diastolic left ventricular dimension of 51 8 mm in 37 adults between 25 and 44 years of age The mean

wall thickness probably reflect deposition of glycosphingolipid in the myocardium

The recent demonstration of biochemical effects of enzyme replacement in Fabry s disease increases the importance of a sensitive noninvasive technique for the assessment of effects of this therapeutic approach[9] Should the disease prove to be reversible, the response to this treatment could be monitored by echocardiographic evidence of regression of abnormal thickness of the left ventricular posterior wall Changes in the aortic root dilatation would be less likely to occur In addition the development of increasing left ventricular wall thickness or aortic root dimension while on replacement therapy would be significant While we detected echocardiographic abnormalities in our patients we do not have sufficient serial studies to determine if echocardiography will be sensitive enough to detect changes in response to therapy

Summary

Fabry s disease results from deficient activity of the enzyme alpha galactosidase A Cardiac abnormalities result from glycosphingolipid deposition in the myocardium valvular tissue and vessel walls A noninvasive method to examine these abnormalities would be useful in the evaluation of patients We examined the echocardiograms of 32 patients 25 hemizygous and seven heterozygous for Fabry s disease

The aortic root diameter was measured in each hemizygote In nine patients under 26 years it was 33 2 ± 1 2 mm and in two it was dilated In 16 patients over 26 years it was 38 8 ± 1 2 mm ($p < 0\ 01$) and in 12 it was dilated The left ventricular posterior wall was measured in the echocardiogram of 21 normotensive hemizygotes The difference in thickness between nine patients under 26 years (9 6 ± 1 3 mm) and 12 patients over 26 years (12 4 ± 07 mm) was not statistically significant Only two of the nine younger patients had left ventricular wall thickness greater than normal compared to eight of the 12 older patients The mean left ventricular shortening fraction of 22 hemizygous patients was normal One hemizygote had echocardiographic evidence of mitral valve prolapse

Four of the seven heterozygotes had normal echocardiograms Among the other three one had increased left ventricular wall thickness a second had disproportionate ventricular septal thickness and a third had both abnormalities. The echocardiographic aortic root size was normal in each heterozygote

Abnormal echocardiographic findings were more common in older hemizygous patients, a distribution similar to that of the age of onset of cardiac dysfunction Increased left ventricular wall thickness probably reflects glycosphingolipid deposition in the myocardium Dilatation of the aortic root may result from degenerative changes of the aortic media Abnormalities of mitral valve echoes were uncommon

REFERENCES

1 Sweeley C C Klionsky B Krivit W and Desnick R J Fabry s disease glycosphingolipid lipidosis in The Metabolic Basis of Inherited Disease edited by Stanbury J B Wyngaarden D S and Fredrickson D S New York 1972 McGraw Hill Book Company Inc p 663 687
2 Ferrans V J Hibbs R G and Burda C D The heart in Fabry s disease a histochemical and electron microscopic study Am J Cardiol 24 95 1969
3 Becker A E Schoorl, R Balk A G and van der Heide R M Cardiac manifestations of Fabry s disease Am J Cardiol 36 829 1975
4 Desnick R J Blieden L C Sharp H L Hofschire P J and Moller J H Cardiac valvular anomalies in Fabry disease clinical morphologic and biochemical studies Circulation 54 818 1976
5 Sahn D J DeMaria A Kisslo J and Weyman A Recommendations regarding quantitation in M mode echocardiography results of a survey of echocardiographic measurements Circulation 58 1072 1978
6 Feigenbaum H in Echocardiography Philadelphia 1976 Lea & Febiger Publishers p 464
7 Gertsenblith G Frederiksen J Yin F C P Fortuin N J Lakatta E G and Weisfeldt M L Echocardiographic assessment of a normal adult aging population Circulation 56 273 1977
8 Guthrie R B and Edwards J E Pathology of the myxomatous mitral valve nature secondary changes and complications Minn Med 59 637 1976
9 Desnick R J Dean K J Grabowski G A Bishop D F and Sweeley C C Enzyme therapy in Fabry disease—differential in vivo plasma clearance and metabolic effectiveness of plasma and splenic alpha galactosidase A isozymes Proc Natl Acad Sci USA 76 5326 1979

greater than 1 3 There was no evidence of systolic anterior motion of the mitral valve or midsystolic closure of the aortic valve on the echocardiograms of any patients

Discussion

Cardiac involvement has long been recognized in Fabry's disease[2] Autopsy studies have described ballooning or interchordal hooding of mitral valve leaflets thickening of the ventricular wall and calcification of the aortic valve leaflets[2] Occasionally abnormalities of the tricuspid valve have also been noted[3] Electron microscopic studies have also shown extensive degeneration of the walls of the ascending aorta These reports have been confined to isolated autopsy cases and the spectrum of involvement in a large group of patients with Fabry's disease has not been reported

Echocardiography allows noninvasive evaluation of patients with Fabry's disease Although chordae tendineae have been described as normal the interchordal hooding in some patients with Fabry's disease[3] is similar to that described in the myxomatous mitral valve[6] Thickening of mitral valve leaflets or a pattern of mitral valve prolapse might be detected on the echocardiogram Thickening of ventricular walls can be easily measured by this technique In addition if degeneration of the ascending aorta results in dilatation this might also be measured from the echocardiogram

A single hemizygote had both an apical late systolic murmur and pansystolic mitral valve prolapse on the echocardiogram Evidence of abnormalities of the mitral valve were not found on the echocardiograms of our other Fabry's patients either heterozygotes or hemizygotes If the abnormality of the mitral valve leaflets described in some autopsy reports in patients with Fabry's disease is common the M mode echocardiogram did not detect it

The aortic root dimension measured by echocardiography increased with age There was a higher incidence of an abnormal aortic root dimension in our older patients and a statistically significant difference in the means of aortic root dimension between the two age groups

The difference in mean left ventricular myocardial thickness between younger and older hemizygous patients was not statistically significant However the incidence of an abnormally thick left ventricular wall was greater in the older patients and their wall thicknesses were greater than a comparable normal population Left ventricular function as estimated by the shortening fraction was normal in our patients

Comparison of our patients with the normal range for echocardiographic aortic root dimension and left ventricular wall thickness described by Feigenbaum seems justified as his subjects were similar to ours in age range (13 to 54 years) and body surface area 1 3 to 2 2 M^2)[6] Aging alone cannot explain the greater aortic root dimensions and left ventricular wall thicknesses in our older hemizygous patients When compared to age matched subjects reported by Gertsenblith and associates[7] our hemizygous patients as a group had greater aortic root dimension and left ventricular wall thickness Neither aortic root dimension nor left ventricular wall thickness correlated with body surface area and the differences in our younger and older patients cannot be explained by differences in patient size

We had only a small number of echocardiograms in heterozygous patients Although one of our seven heterozygous patients was clinically affected each had normal mitral valve echoes and normal aortic root dimensions The left ventricular posterior wall thickness was increased on the echocardiograms of two of the heterozygous patients only one of whom was clinically affected (this latter patient also had disproportionate ventricular septal thickening)

The M mode echocardiogram allowed us to detect abnormalities of aortic root dimension and left ventricular wall thickness in many but not all of our patients with Fabry's disease Abnormal echocardiographic findings were more common in older hemizygous patients and this distribution is similar to the common onset of cardiac dysfunction in the third and fourth decade of life The degenerative changes described by Becker and associates[3] in the aortic media may explain the increased aortic root dimensions in some patients Dissecting aneurysms however have not been a problem in our patients nor has this complication been reported by others The absence of mitral valve abnormalities on the echocardiogram may mean that structural abnormalities in mitral valve leaflets are not common in patients with Fabry's disease or that the changes are not significant enough to be detected by echocardiography Increases in left ventricular

Table 1 Background data on patients in the study

Extent of disease	Number of patients	Mean age	Reason for catheterization: Typical angina pectoris	Atypical angina pectoris	Other	Resting ECG: Normal	Abnormal	Infor- on ECG
0 vessel	13	48	6	6	1	10	3	0
1 vessel	14	51	7	5	2	4	10	5
2 vessel	15	51	9	3	2	3	12	1
3 vessel	8	50	6	1	1	2	6	3

changes in position[10-12] patients were monitored at the beginning of each ambulatory ECG recording in six standardized positions (prone supine left side right side sitting and standing) ECG s were also recorded with hyperventilation and Valsalva maneuver neither of which caused any ECG changes in the group of patients studied Calibration signals were provided at the beginning of each recording by a millivolt calibrator (Del Mar Avionics Irvine Ca, Model No 456)

ECG lead system After preparation of the skin Exerstress (Del Mar Avionics Irvine, Ca) electrodes were firmly attached at the positions of CC5 (positive electrode fifth intercostal space anterior axillary line on the left negative electrode in corresponding position on the right) and modified aV_F (positive electrode below the xyphoid process negative electrode beneath the mid left clavicle) The ground electrode was positioned on the right flank The modified aV_F was found to closely resemble aV_F on scalar ECG s in 20 patients in whom both of these leads were placed and compared In this group the R/S ratio of modified aV_F was 82% of the R/S ratio in scalar aV_F Lead CC5 has been shown in the past to closely resemble Lead V_5 on scalar ECG s[1]

Ambulatory ECG tapes were evaluated using a dynamic electrocardioscanner (Del Mar Avionics Irvine Ca Model No 660A) Average heart rate in each patient was determined by the total number of beats per 24 hours divided by 1 440 minutes per day If any artifacts were noted during the scanning the beats counted and time elapsed during that period were excluded from analysis Random recordings each lasting six seconds were obtained at 15 minute intervals during the day (97 recordings per 24 hours) Each random recording was analyzed for ST segment deviations and considered positive if the ST segment was deviated more than 1 mm greater than any positional ST segment change noted on baseline recordings persisting for at least 0 08 sec from the J point in at least three consecutive beats This criterion is commonly used in exercise testing[14]

In addition the extent of ST segment deviation on the ambulatory ECG was compared with that of simultaneously recorded scalar ECG s during exercise testing in 23 different patients during another study ST segment deviations were within 0 25 mm by both methods

Times of day of all ST segment deviations were noted and were compared with entries in the patient s diaries which were completed very compulsively by the majority of study patients. ST segment deviations in association with symptoms or occurring five minutes before or after symptoms were excluded from analysis and were considered separately The number of recordings with silent ST segment deviations was divided by the total number of recordings during the 24 hours to determine the percentage of observations in which silent ST segment deviations occurred Heart rate during all deviations was recorded The extent of ST segment deviations was measured independently by two observers without knowledge of angiographic findings

Angiography Coronary angiography and ventriculography were performed by using the Sones technique[5] Angiograms were analyzed in two views and were considered to reveal significant coronary artery disease if any major vessel had greater than 70% luminal diameter narrowing in one plane or greater than 50% luminal diameter narrowing in two planes Patients were then divided into groups with one two and three vessel disease Patients with normal coronary arteries and those with less than 70% luminal diameter narrowing in any major artery were considered to have zero vessel disease The results showed no difference between the subgroups of patients making up the group with zero vessel

Silent ST segment deviations and extent of coronary artery disease

Steven H Kunkes M D
Augusto D Pichard M D F A C C
Harry Smith Jr Ph D
Richard Gorlin M D F A C C
Michael V Herman M D F A C C
Joel Kupersmith M D F A C C
New York N Y

The clinical diagnosis of myocardial ischemia in ambulatory patients is usually based on a history of typical angina pectoris However myocardial ischemia occurs without pain and painless ST segment deviation as sometimes occurs during exercise testing may indicate the presence of asymptomatic coronary artery disease There have been relatively few reports to delineate the prevalence of clinically silent ST segment deviations in ambulatory patients during routine activities rather than during exercise testing The significance of such changes is as yet unknown and it is unclear to what extent they occur in apparently normal patients

We studied 50 patients both with and without coronary artery disease as demonstrated by coronary angiography to determine the extent of silent ST segment deviations during routine daily activity We determined the relationship of the latter to the presence and severity of coronary artery disease and to ventricular function and heart rate

Methods

Patient population After obtaining informed consent we studied 50 patients all of whom had cardiac catheterization and left ventricular angiography to evaluate typically ischemic chest pain (27 patients) or atypical chest pain (16 patients) or to evaluate coronary anatomy after myocardial infarction syncopal episodes or episodic dyspnea (seven patients) Atypical chest pain was defined as a sticking or stabbing chest pain which was not regularly precipitated by exertion The sample population consisted of 39 men ages 31 to 68 and 11 women ages 39 to 53 Patients with a left bundle branch block valvular lesion metabolic abnormality (abnormal calcium or potassium levels thyroid disease) or inability to ambulate were excluded Patients with mitral valve prolapse and those with hypertrophic cardiomyopathy were also excluded Twenty six patients were receiving propranolol in doses of 40 to 160 mg per day (average dose 100 mg daily) One patient was receiving propranolol in a dose of 320 mg per day and 25 patients were receiving either nitroglycerin or isosorbide dinitrate in doses of 10 to 40 mg per day at the time of the study Five patients had received digoxin 0 25 mg per day until the day of the study

Monitoring periods Each patient was monitored with a two channel ambulatory ECG (Del Mar Avionics Irvine Ca Model No 445) for 24 hours before or after cardiac catheterization During monitoring patients were instructed to perform their routine daily activities and to keep thorough diaries detailing stressful or unusual activities times of meals rest periods and any experience of discomfort To determine any changes in the ST segment which occurred due to

From the Divisions of Cardiology and Clinical Pharmacology Department of Medicine and Department of Biostatistics Mount Sinai Medical Center New York N Y

Received for publication Jan 30 1980
Accepted for publication April 1980

Reprint requests Steven H Kunkes M D Internal Medicine Associates of Fairfield P C 1305 Post Rd Fairfield CT 06430

0002-8703/80/100813 + 08$00 80/0 © 1980 The C V Mosby Co

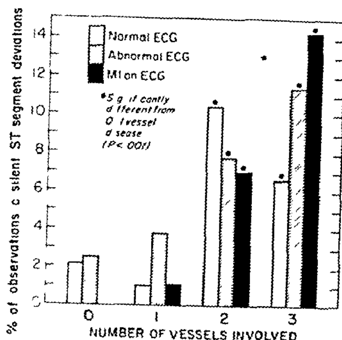


Fig 2 Effect of the resting ECG on the correlation of the prevalence of silent ST segment deviations and the extent of coronary artery disease *Clear bars* represent normal resting ECG s *hatched bars* represent abnormal resting ECG s and *black bars* represent old myocardial infarction on the resting ECG Silent ST segment deviations correlated with the extent of coronary artery disease regardless of the resting ECG There was no significant difference in the prevalence of silent ST segment deviations within each class of coronary disease regardless of the resting ECG

typical and atypical chest pain were analyzed separately and this variable did not affect results

Silent ST segment deviations and resting ECG Patients in each group presenting with normal and abnormal resting ECG s as well as those with old myocardial infarction on resting ECG are shown in Table I When patients with normal and abnormal resting ECG s were analyzed separately this variable was found not to affect results (Fig 2)

Silent ST segment deviations and pharmacologic therapy The number of patients receiving propranolol is shown in Table II As might be expected since more severely ill patients were more likely to receive treatment this number increased with severity of disease Propranolol therapy might be expected to decrease the occurrence of silent ST segment deviations In this study propranolol did not significantly affect the relationship between prevalence of silent ST segment deviations and the extent of coronary artery disease ($p > 0.05$) (Fig 3) Though there were numerical differences in the prevalence of silent ST segment deviations between patients with and without propranolol within each group this difference was not statistically significant Patients being treated with propranolol had an average heart rate of 67 beats per minute while those without propranolol averaged 72 beats per minute Propranolol may never have been given to full beta blockade

Table II also shows the percentage of patients in each disease category who were receiving nitrates Nitrate therapy did not affect the prevalence of ST segment deviations (Fig 3) Numerical differences in the prevalence of silent ST segment within each group were found for patients with and without nitrate therapy but these differences were not statistically significant We did not attempt to alter drug regimens of patients in our study and therefore patients were not receiving nitrates in any standard protocol

Five patients were receiving digitalis preparations and these patients were only in the two and three vessel disease groups Although dig is may clearly influence ST segments during exercise testing causing false positive tests the differences in the percent of observations in 24 hours with silent ST segment deviations between groups was not influenced when patients receiving digitalis were excluded

Silent ST segment deviations and left ventricular function There was no relationship between silent ST segment deviations and the presence and degree of wall motion abnormalities Normal or abnormal ejection fraction was also unrelated

Silent ST segment deviation and heart rate Increased heart rate was defined here as 10 beats per minute above the average daily heart rate In the zero vessel disease group 60% of silent ST segment deviations occurred at increased heart rates and therefore may have been rate rel However in the one two and three-vessel disease groups only 34% 7% and 25% respectively of silent ST segment deviations occurred at heart rates higher than 10 beats per minute above the average daily heart rate Therefore the majority of ST segment deviations did not appear to be rate related

ST segment deviations associated with pain No patient with zero vessel or one-vessel disease had any observations of ST segment deviation which were associated with pain as noted in the patient s diary Six percent of observations of ST

Table II Numbers of patients displaying silent ST segment deviations and receiving medications

Extent of disease (no of pts)	*Number displaying silent ST segment deviations*	*Number receiving propranolol*	*Number receiving nitrates*
0 vessel (13)	5	3	6
1 vessel (14)	7	6	5
2 vessel (15)	15	12	10
3 vessel (8)	8	7	5

disease Angiographic interpretation was performed without knowledge of the results of ambulatory ECG analysis

For evaluation of ventricular function segmental motion analysis[16] of the left ventriculogram was made and the resting ejection fraction was determined Wall motion abnormalities were expressed as being dyskinetic akinetic and hypokinetic and the percent of the perimeter of the left ventricular silhouette with abnormal wall motion was determined

Statistical analysis The patients were divided into four groups zero one two and three vessel disease The percent of silent ST segment deviation per patient was recorded and transformed using an arcsin transformation Comparisons among the four groups were made using the analysis of variance and Duncan's multiple range procedure All statistical tests were done using a P level of < 0.05

Results

The number of patients in each group their ages reason for catheterization and resting ECG are shown in Table I The percentage of patients who displayed any silent ST segment deviations is shown in Table II Thirty eight percent of patients with nonobstructive disease and 50% of patients with one vessel involvement displayed these changes All patients with two and three vessel disease had silent ST segment deviations

Fig 1 shows for each group the percentage of observations in which ST segments shifted This percentage increased with the increasing extent of coronary artery disease The group with zero vessel disease had silent ST segment deviations an average of 2.2 ± 1.0% of observations in 24 hours one vessel disease had silent ST segment deviations 2.9 ± 1.8% of observations in 24 hours

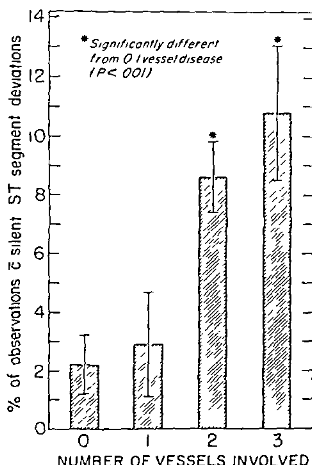


Fig 1 Correlation of silent ST segment deviations with the extent of coronary artery disease *Hatched bars* represent the percentage of observation with silent ST segment deviations on the ambulatory ECG for each grade of coronary artery disease Note how this percentage increases with the extent of coronary artery disease See text for further discussion

two vessel disease 8.2 ± 1.0% of observations in 24 hours and three vessel disease 10.1 ± 2.4% of observations in 24 hours The difference in the percent of observations with silent ST segment deviations during 24 hours between zero and one vessel disease groups when compared with the two and three vessel disease groups was significant ($p < 0.001$) while other differences were not

The following factors had no influence on the correlation between percent of observations of silent ST segment deviations and the extent of coronary artery disease

Silent ST segment deviations and precatheterization symptoms Table I shows the occurrence of typical and atypical chest pain with varying extent of coronary artery disease Patients with

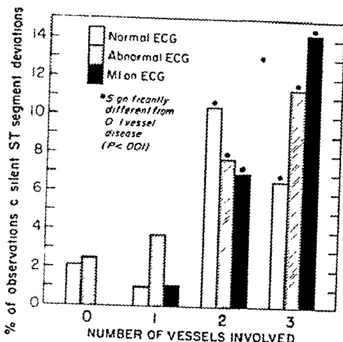


Fig 2 Effect of the resting ECG on the correlation of the prevalence of silent ST segment deviations and the extent of coronary artery disease *Clear bars* represent normal resting ECG s *hatched bars* represent abnormal resting ECG s and *black bars* represent old myocardial infarction on the resting ECG Silent ST segment deviations correlated with the extent of coronary artery disease regardless of the resting ECG There was no significant difference in the prevalence of silent ST segment deviations within each class of coronary disease regardless of the resting ECG

typical and atypical chest pain were analyzed separately and this variable did not affect results

Silent ST segment deviations and resting ECG Patients in each group presenting with normal and abnormal resting ECG s as well as those with old myocardial infarction on resting ECG are shown in Table I When patients with normal and abnormal resting ECG s were analyzed separately this variable was found not to affect results (Fig 2)

Silent ST segment deviations and pharmacologic therapy The number of patients receiving propranolol is shown in Table II As might be expected since more severely ill patients were more likely to receive treatment this number increased with severity of disease Propranolol therapy might be expected to decrease the occurrence of silent ST segment deviations In this study propranolol did not significantly affect the relationship between prevalence of silent ST segment deviations and the extent of coronary artery disease ($p > 0.05$) (Fig 3) Though there were numerical differences in the prevalence of silent ST segment deviations between patients with and without propranolol within each group the difference was not statistically significant Patients being treated with propranolol had an average heart rate of 67 beats per minute while those without propranolol averaged 7? beats per minute Propranolol may never have been given to full beta blockade

Table II also shows the percentage of patients in each disease category who were receiving nitrates Nitrate therapy did not affect the prevalence of ST segment deviations (Fig 3) Numerical differences in the prevalence of silent ST segment within each group were found for patients with and without nitrate therapy but these differences were not statistically significant We did not attempt to alter drug regimen of patients in our study and therefore patients were not receiving nitrates in any standard protocol

Five patients were receiving digitalis preparations and these patients were only in the two and three vessel disease groups Although digitalis may clearly influence ST segments during exercise testing causing false positive test the differences in the percent of observations in 24 hours with silent ST segment deviations between groups was not influenced when patients receiving digitalis were excluded

Silent ST segment deviations and left ventricular function There was no relationship between silent ST segment deviations and the presence and degree of wall motion abnormalities Normal or abnormal ejection fraction was also unrelated

Silent ST segment deviation and heart rate Increased heart rate was defined here as 10 beats per minute above the average daily heart rate In the zero vessel disease group 60% of silent ST segment deviations occurred at increased heart rates and therefore may have been rate related However in the one two and three vessel disease groups only 34% 7% and 25% respectively of silent ST segment deviations occurred at heart rates higher than 10 beats per minute above the average daily heart rate Therefore the vast majority of ST segment deviations did not appear to be rate related

ST segment deviations associated with pain No patient with zero vessel or one-vessel disease had any observations of ST segment deviations which were associated with pain as noted in the patient s diary Six percent of observations of ST

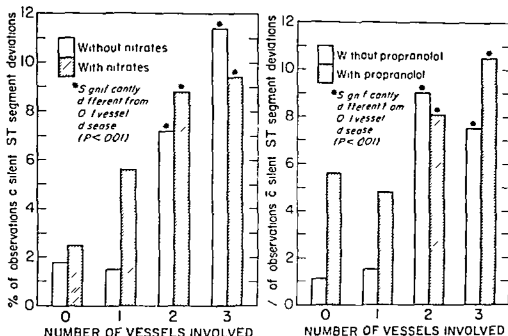


Fig 3 Lack of influence of propranolol and nitrate therapy in the doses used on the correlation of the prevalence of silent ST segment deviations with the extent of coronary artery disease *Vertical axis* represents the percentage of observations in 24 hours with ST segment deviations *Hatched bars* represent patients receiving medications (see text for dose) Silent ST segment deviations correlated with the extent of coronary disease regardless of propranolol or nitrate therapy in these doses. Though there were numerical differences in the prevalence of ST segment deviation between patients with and without medications within each class of disease the differences were not statistically significant

segment deviation in the two vessel disease group and 3% of observations in the three vessel disease group were associated with pain and these observations were excluded from analysis

Discussion

Clinically coronary artery disease usually presents with angina pectoris or with catastrophic events such as myocardial infarction or sudden death Our study suggests however that in addition to these manifestations there are regular and frequent dynamic electrocardiographic changes (ST segment deviations) which may reflect underlying recurrent myocardial ischemia as has been suggested previously[6, 9] Pain is only one of the clinically recognizable responses to ischemia and the frequency of silent ST segment deviations suggests that painless ischemia occurs frequently in patients with obstructive coronary artery disease Furthermore the frequency of these ST segment deviations on the ambulatory ECG correlates with the severity of the coronary artery disease Though no significant difference was noted between patients with nonobstructive coronary artery disease and one vessel disease or between two and three vessel disease there was a markedly significant difference ($p < 0.001$) between the zero and one and two and three vessel disease groups This difference was not influenced by the patient s symptoms resting ECG or ventricular function but only by the number of coronary arteries occluded Also since most ST segment deviations occurred at heart rates within 10 beats per minute of the average heart rate the deviations were probably not rate related

Previous studies of silent ST segment changes on the ambulatory ECG have been consistent with our observations in showing that they occur more commonly in patients with clinical coronary artery disease[6, 7] that they may have prognostic significance[7] and that they can occur during driving and sleep[6] However comparison of silent ST segment deviations on the ambulatory ECG with the extent of angiographically proven coronary artery disease has not been previously made

In studies using the ambulatory ECG it is important to properly evaluate the lead system used Ambulatory ECG systems use bipolar chest leads and differ both from conventional ECG

monitoring of active subjects Br Heart J 36 481 1974

18 Froelicher V F Wolthuis R Stewart A Keiser N Fischer J Longo M R Triebwasser J H and Lancaster M C A comparison of two bipolar exercise electrocardiographic leads to lead V Chest 70 611 1976

19 Bellet S and Muller O F Electrocardiogram during exercise Its value in the diagnosis of angina pectoris Circulation 32 477 1975

20 Maseri A L'Abbate A Baroldi G Chierchia S Marzilli M Ballestra M A Severi S Parodi O Biagini A Distant A and Pesola A Coronary vasospasm as a possible cause of myocardial infarction N Engl J Med 299 1271 1978

21 Haeren J W Sudden coronary death The occurrence of platelet aggregates in the epicardial arteries of man Atherosclerosis 14 417 1971

22 Gorlin R Physiology of Myocardial Blood Flow and Metabolism in Coronary Artery Disease Vol XI in the series Major Problems in Internal Medicine Smith L H Jr ed Philadelphia 19 6 W B Saunders Company pgs 71-86

23 Kupersmith, J Electrophysiologic and electrocardiographic aspects of myocardial ischemia including stress testing in Angina Pectoris Donoso E and Gorlin R eds New York 19 Stratton Intercontinental Medical Book Corporation pgs 28 44

24 Alderman E Coltart D J Wettach G W and Harrison D C Coronary artery syndromes after sudden propranolol withdrawal Ann Intern Med 81 [illegible] 1974

25 Goldschlager N Selzer A and Cohn K Treadmill stress tests as indicators of presence and severity of coronary artery disease Ann Intern Med 85 [illegible] 1976

most false negative exercise tests occur in patients with one vessel disease.[5] Also we stress that it is not the presence of ST segment deviations but rather the total duration of ST segment deviations over 24 hours which correlates with more severe degrees of coronary disease. Ultimately though, since we are unsure of the actual cause of ST segment deviations, we cannot state why more silent ST segment deviations were not seen in patients with one vessel disease.

In the present study, there were few episodes of ST segment deviation associated with the subjective experience of pain. The use of patient diaries has certain limitations, though the importance of keeping complete records was stressed and was carried out. It is possible as well that patients voluntarily curtailed their activities because of the monitoring procedure. It must also be considered that the pharmacotherapy the patients received may have suppressed pain without altering the electrocardiographic determinants of ischemia. This may have been a function of inadequate therapy, as mentioned above.

Because painless ST segment deviations on the ambulatory ECG are relatively frequent in patients with coronary artery disease, reversal of ST segment deviations may provide a more definite end point of therapy to reverse ischemia than either relief of pain or exercise testing. This technique may also be used to evaluate drug or surgical therapy.

The occurrence of frequent silent ST segment deviations in patients with two and three vessel coronary artery disease may reflect an important underlying process that is undetectable without specific and proper testing.

Summary

Fifty patients who underwent coronary and left ventricular angiography for suspected coronary artery disease (CAD) had ambulatory ECG monitoring at a time remote from that of catheterization. After correcting for positional ST segment variation on ambulatory ECG, the amount of time that ST segments deviated more than 1 mm from baseline without corresponding angina was determined, and these results were correlated with results of angiography. Silent ST segment deviations were seen in patients without significant CAD in 2.2% of observations, but increased significantly with extent of coronary artery disease (2.9%, 8.2%, and 10.1% of observations in the one, two, and three vessel disease groups, respectively). This relationship was independent of ventricular function, resting ECG, and previous symptoms. It is concluded that silent ST segment deviations on ambulatory ECG reflect the presence and severity of coronary artery disease.

REFERENCES

1. Master A M: The Master two-step test. AM HEART J 75:809, 1968.
2. Ellestad M H, Allen W, Wan M C K, and Kemp G L: Maximal treadmill stress testing for cardiovascular evaluation. Circulation 39:517, 1969.
3. Kattus A A, Jorgensen C R, Worden R E, and Alvero A B: ST segment depression with near maximal exercise in detection of preclinical coronary heart disease. Circulation 44:585, 1971.
4. Froelicher V F, Thompson A J, Longo M R, Triebwasser J H, and Lancaster M C: Value of exercise testing for screening asymptomatic men for latent coronary artery disease. Progr Cardiovasc Dis 18:265, 1976.
5. Redwood D R, Borer J S, and Epstein S E: Whither the ST segment during exercise? (Editorial) Circulation 54:703, 1976.
6. Bellet S, Roman L, Kostis J, and Slater A: Continuous electrocardiographic monitoring during automobile driving. Am J Cardiol 22:856, 1968.
7. Stern S, and Tzivoni D: Dynamic changes in the ST-T segment during sleep in ischemic heart disease. Am J Cardiol 32:17, 1973.
8. Allen R D, Gettes L S, Phalan C, and Avington M D: Painless ST segment depression in patients with angina pectoris. Chest 69:467, 1976.
9. Schang S J, and Pepine C J: Transient asymptomatic ST segment depression during daily activity. Am J Cardiol 39:396, 1977.
10. Lachman A B, Semler H J, and Gustafson R H: Postural ST-T wave changes in the radioelectrocardiogram simulating myocardial ischemia. Circulation 31:557, 1965.
11. Hinkle L E, Meyer J, Stevens M, and Carver S T: Tape recordings of the ECG of active men. Circulation 36:753, 1967.
12. Krasnow AZ, and Bloomfield D K: Artifacts in portable electrocardiographic monitoring. AM HEART J 91:349, 1976.
13. Blackburn H, Taylor H L, Okamoto N, Rautaharju P, Mitchell P L, and Kerkhof A C: Standardization of the exercise electrocardiogram. A systematic comparison of chest lead configurations employed for monitoring during exercise. *In* Physical Activity and the Heart, Karvonen M J, and Barry A J, eds. Springfield, Illinois, 1967, Charles C Thomas Publisher, pgs 101-133.
14. Ellestadt M: Stress Testing Principles and Practices. Philadelphia, 1975, F A Davis Company, pg 96.
15. Sones F M, Shirey E K, Proudfit W L, and Westcott R: Cine coronary arteriography (Abst.) Circulation 20(Suppl.):773, 1959.
16. Herman M V, Heinle R A, Klein M D, and Gorlin R: Localized disorders in myocardial contractility—asynergy and its role in congestive heart failure. N Engl J Med 277:222, 1967.
17. Stern S, and Tzivoni D: Early detection of silent ischemic heart disease by 24 hour electrocardiographic

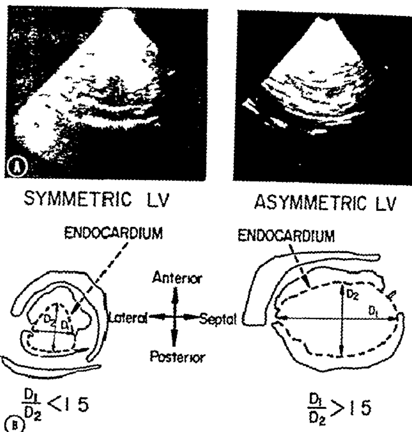


Fig 1 *A* Polaroid photographs of typical echocardiographic short axis images from two formalin fixed ventricles. On the *left* is a symmetric ventricle and on the *right* is an asymmetric ventricle *B* A diagrammatic sketch illustrates the orientation of these images The anterior wall is above posterior wall below septal wall to the right, and lateral wall to the left Diameters are measured as shown from septal to lateral (D_1) and from anterior to posterior (D_2) The approximate endocardial border is outlined by the *broken line*

sary to avoid shrinkage of the LV (left ventricular) cavity during formalin fixation and to induce either symmetry or asymmetry into the ventricular chamber Nine left ventricles were stuffed in such a manner that the septal lateral diameter was more than 1 5 times the anterior posterior diameter The formalin fixed left ventricles were immersed in mineral oil and were viewed with the phased array sector scanner to obtain cross sectional images (Fig 1) similar to images described in echo studies of the closed chest dogs Six to ten short axis cross sections were obtained from base to apex by moving the transducer in the mineral oil over the left ventricle Long axis cross-sections were obtained by rotating the transducer 90 degrees All views were recorded on videotape and were subsequently played back for analysis Following the echocardiographic procedures the left ventricle was removed from the mineral oil rinsed thoroughly and was filled from a graduated cylinder up to the mitral and aortic valve rings with a known amount of mineral oil This rinsing and filling procedure was performed three times and an average was obtained for the fluid volume of the left ventricular chamber the fluid volume served as the known standard for comparison with echocardiographic determination of volume

Determination of LV volume Using cross sectional echocardiographic images, five mathematical models were tested by comparison of calculated left ventricular volume versus true volume A linear regression analysis was performed on nine asymmetric ventricles and on 1? symmetric ventricles Endocardial outlines were traced from projections of short axis and long axis cross sections during videotape stop-motion replay As is evident from Figs. 1 and 2 echocardiographic short axis and long axis images are characterized by strong circumferential echoes at the endocardial interfaces By tracing at the inner border of these circumferential echoes, the thickness of the endocardial echo is excluded from the endocardial area This procedure of tracing the

Experimental and laboratory reports

Cross sectional echocardiography III Analysis of mathematic models for quantifying volume of symmetric and asymmetric left ventricles

Horace L Wyatt Ph D
Samuel Meerbaum Ph D
Ming K Heng M D
Pascal Gueret M D
Eliot Corday M D
Los Angeles Calif

Previous clinical studies on left ventricular volumes[1-4] have shown that M mode echocardiography correlates well with angiography for patients with normal myocardial wall motion but not for those with regional myocardial dyssynergy The cube method of M mode echo utilizes only one diameter measurement and is derived from the formula for the volume of a symmetrical ellipsoid Thus inaccuracies of volume quantification should accompany any ventricular asymmetry due to regional dyssynergy

Recently techniques were developed in this laboratory for performing noninvasive cross sectional echocardiography in closed chest dogs[5] With this technique a variety of left ventricular cross sectional images may be recorded for detailed analysis of cardiac size structure and function this development represents a definite improvement over the one-dimensional measuring capabilities of M mode echocardiography

From the Department of Medicine Division of Cardiology Cedars-Sinai Medical Center and the Department of Medicine UCLA School of Medicine Los Angeles, Calif rn

Supported in part by Grant HL 17651-04 from the National Heart Lung and Blood Institute National Institutes of Health, Bethesda Maryland 20014 the American Heart Association Greater Los Angeles Affiliate Mrs Anna Bing Arnold Mrs Loren M y r Nid rf the J les Stein Foundation and the Florence P Hamilton Foundation Los Angeles, California Partial support from NASA 7 100 California Institute of Technology Jet Propulsion Laboratory is also acknowledged.

Received for publication July 5 1979

Accepted for publication Oct 19 1979

Reprint requests Dr Eliot Corday Cedars-Sinai Medical Center Halper Bldg Room 301 8700 Beverly Blvd., Los Angeles, Calif 90048.

Previous cross sectional echocardiographic studies from this laboratory demonstrated that left ventricular mass in the closed chest dog[7] and left ventricular volume in the formalin fixed heart[8] may be quantified best with mathematical models incorporating short axis area measurements However the adequacy of cross sectional echocardiography for quantification of left ventricular volume in the presence of substantial ventricular asymmetry has not been investigated Thus a study of cross-sectional echocardiography was designed to investigate the influence of asymmetry on volume quantification in formalin fixed canine left ventricles Echocardiographic cross sectional images were obtained and mathematical models were utilized similar to those for in vivo studies of the left ventricle[7]

Methods

Cross sectional echocardiographic studies were performed with an electronic phased array sector scanner (Varian Associates Palo Alto CA) Features of this system include real time high resolution a 32 element transducer an 84 degree sector angle and a videotape recording rate of 30 frames per second The 84 degree sector angle facilitates recording of entire cross sections of the left ventricle in short axis or long axis orientations

Nineteen dogs were killed with an overdose of anesthetic and their hearts were removed left ventricles were separated from the rest of the heart stuffed with gauze and fixed in formalin for at least 3 days Insertion of gauze was neces

CROSS-SECTIONAL ECHOCARDIOGRAPHY
MATHEMATICAL MODELS FOR LV VOLUME

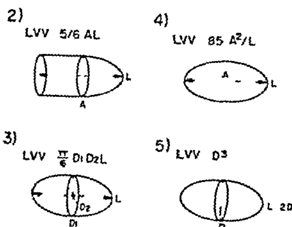


Fig 4 This figure illustrates four of the mathematic models that were utilized in this study Each formula is accompanied by a geometric figure from which the formula was derived Model 2 on the upper left shows that with endocardial area *(A)* from only one short axis cross-section and the length *(L)* from one long axis cross-section left ventricular volume may be calculated by the formula shown $V = 5/6\ AL$, which is represented by the figure shown a half cylinder half ellipsoid Model 3 on the lower left shows that with both minor axis diameters from one short axis section and left ventricular length *(L)* from a long axis section, the volume of an ellipsoid may be computed by $V = \pi/6\ D_1 D_2 L$, where D_1 = septal to lateral diameter D_2 = anterior to posterior diameter This is a standard ellipsoidal formula that has been utilized previously with cineangiography for left ventricular volume determination. With Model 4 on the upper right, the volume of an ellipsoidal figure is calculated by the standard angiographic area length formula $V = 0.85\ A^2/L$ this formula utilizes both the area *(A)* and the length *(L)* from a long axis section of the left ventricle With Model 5 on the lower right the volume of an ellipsoidal figure is calculated with the cube method formula $V = D^3$ developed specifically for M mode echocardiography D = septal lateral diameter of the left ventricle

Mathematical models

Model 1 (Fig 3) Length (L) was divided by the number of short axis sections to obtain an arbitrary height (h) for each short axis section Left ventricular volume was then calculated by a short axis reconstruction procedure using Simpson's rule based upon short axis areas (A) and heights Volume for the apical section was calculated by the formula for an ellipsoidal volume segment shown as the last two terms in the ventricular volume formula at the bottom of Fig 3 Volumes for each remaining short axis section were calculated simply by multiplying the respective area (A) of the section by height (h) Ventricular endocardial volume (V) is obtained by summation of the section volumes,

$$V = A_1 h + A_2 h + A_3 h + \frac{A_4 h}{2} + \frac{[illegible] h^3}{6}$$

Model 2 (Fig 4) The volume (V) of a cylinder may be simply calculated by multiplying the area (A) from a single left ventricular short axis section at the low papillary muscle level with the left ventricular length (L) determined from a long axis section $V = AL$ The volume of the ellipsoid is calculated from the same parameters i.e. A and L using the following derivation $V = 4/3\pi\ r_1 r_2 r_3$ for a nonprolate ellipsoid where r_1, r_2 and r_3 are the respective radii assuming $A = \pi r_1 \times r_2$ and $L = 2r_3$, $V = 2/3\ AL$ Thus the only difference between the volume formulas for ellipsoid and cylinder models is a constant (2/3) Since the left ventricle may be represented by a shape that is ellipsoidal toward the apex and cylindrical toward the base (Fig 4A *top left panel*) the volume formula for Model 2 was approximated by averaging the constants for the ellipsoid and cylinder models $V = 5/6\ AL$

Model 3 (Fig 4) The volume of an ellipsoid is calculated from the left ventricular length (L) and both minor axis diameters determined from a short axis echocardiographic section at the low papillary muscle level D_1 = septal to lateral diameter D_2 = anterior to posterior diameter The formula for the volume of an ellipsoid is $V = 4/3\ \pi\ r_1\ r_2\ r_3$ if $D_1 = 2r_1$ $D_2 = 2r_2$ and $L = 2r_3$ then $V = \pi/6\ D_1\ D_2 L$ This standard ellipsoidal formula has been utilized previously for left ventricular volume by cineangiography

Model 4 (Fig 4) Volume of an ellipsoidal figure may be calculated by the standard angiographic area length formula utilizing the area (A_L) and the length (L) both from a long axis section of the ventricle Using $V = 4/3\ \pi\ r_1\ r_2\ r_3$ one assumes $r_1 = r_2$, $r_3 = L/2$ and $A_L = \pi r_1 (L/2)$ Then $r_1 = r_2 = 2A_L/\pi L$ $V = 4/3\pi (2A_L/\pi L)^2 (L/2) = 0.85\ A_L{}^2/L$

Model 5 (Fig 4) Volume of an ellipsoidal figure may be calculated with the cube formula developed specifically for M mode echocardiography This method uses the septal to lateral diameter (D) of the left ventricle measured at the low papillary muscle level If $V = 4/3\pi\ r_1\ r_2\ r_3$ and $r_1 = r_2 = D/2$ and r_3 is assumed $= D$ then $V = D^3$

Data analysis In 19 formalin fixed left ventr





Fig 2 *A* Polaroid photograph of a typical echocardiographic long axis image from a formalin fixed left ventricle *B* A diagrammatic sketch illustrates the orientation of this image Above is the anterior wall below the posterior septum to the right is the base and to the left is the apex Length is measured from apex to base as indicated The approximate endocardial border is outlined by the *broken line*

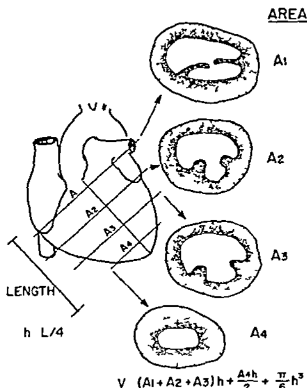


Fig 3 Sectional analysis of the left ventricle (LV) in dogs with the phased array sector scanner Short axis cross-sectional views are obtained at four to eight levels from the base to the apex Shown here are (1) mitral valve section (A1 = area of endocardial surface) (2) high papillary muscle section (A2 = area) (3) low papillary muscle section (A3 = area) (4) apical section (A4 = area) LV length *(L)* obtained from a long axis view (apex to mitral-aortic junction) is divided by the number of short axis sections to give an arbitrary height *(h)* for each section Volume *(V)* of the chamber is calculated by Simpson s rule for summation of area height for each section except the apical section the volume of which is calculated with the formula for an ellipsoidal segment

inner echo borders was found to carry smaller interobserver variability than tracing at the center of the endocardial echo Linear measurements were obtained from the cross-sectional outlines and areas enclosed within the outlines were obtained by planimetry Length of ventricles was measured in the long axis section (Fig 2) as the distance from apex to the mitral ring at the base In a previous study of two D echo in dogs left ventricular short axis diameter and area measurements in several simplified mathematic models were based on a section taken at the high papillary muscle level Formalin fixation procedures in this study resulted in some constriction of the chamber lumen at the base of the LV so that the high papillary section was not always representative of the LV Thus with formalin fixed left ventricles the short axis section at the low papillary muscle level two thirds of the distance between the base and apex was utilized for the simplified models[2]

Calibration of cross sectional echocardiographic measurements was performed from scales along the horizontal and vertical axes of the images predetermined in the system used (Varian Inc) from precise fixed-distance calibrations. These calibrations were subsequently checked in our laboratory and were found to be accurate However the calibration scale was rechecked for each echocardiographic measurement since some variation may occur with changes in gain settings and variation in calibration may also occur over the range of the screen The calibrations were measured during videotape motion replay to allow better visualization of the scale Calibration factors were determined and were applied to each volume calculation

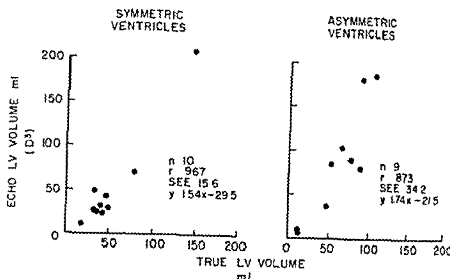


Fig 6 Comparison of volume in formalin fixed left ventricle cross sectional echocardiography (cube method, Model 5) on the Y axis versus true volume on the X axis A linear regression analysis was performed for calculated ersus true volume the regression equation is shown The correlation coefficient was excellent for symmetric ntricles (n = 10) but substantially lower for asymmetric (n = 9) ventricles 0 967 and 0 873 respectively N = number of ventricles r = correlation coefficient SEE = standard error of estimate

Table I Summarized results of linear regression and percent error analyses for echocardiographic volume versus true volume utilizing 5 mathematic models

	REC	5/6 AL	π/6 D D₁L	0 85 A /L	D'
10 symmetric ventricles					
Model	1	2	3	4	5
r	0 996	0 993	0 984	0 972	0 967
M	0 98	1 34	0.98	0 81	1.54
I	+0 94	−12 0	−10 88	+0 03	−29 46
SEE	3 37	6 13	6 81	7.52	15.56
MPE	5 9 ± 1 2	10 1 ± 3 0	26 6 ± 3 1	30 9 ± 4 8	29.6 42
9 asymmetric ventricles					
Model	1	2	3	4	5
r	0 985	0 974	0 956	0.886	0.873
M	0 95	1 11	0 69	0 48	1 74
I	+0 57	−9 04	−0 97	+2 19	−21 48
SEE	5.83	9 09	7.53	8 93	34.27
MPE	9 8 ± 2 8	20 3 ± 9 0	35 4 ± 5 0	5?1 ± 3 0	53 5 + 13 4

REC = reconstruction using Simpson s rule r = correlation coefficient M = slope I = intercept SEE = standard error of estimate MPE = mean percent error

significantly from corresponding values for Model 1 With Model 3 (Table I) the short axis diameter length method correlation coefficients were also excellent for both symmetric and asymmetric ventricles 0 984 and 0 956 respectively Mean percent errors were 26 6% and 35 4% respectively Only the correlation coefficient for symmetric ventricles was significantly lower for Model 3 than for Model 2 other values were not significantly different With Model 4 (Table I) the long axis area length method the correlation coefficient was excellent for symmetric ventricles 0 972 but was substantially lower for asymmetric ventricles 0 886 the latter value was also significantly lower than the corresponding value for Model 3 Mean percent errors were 30.9% for

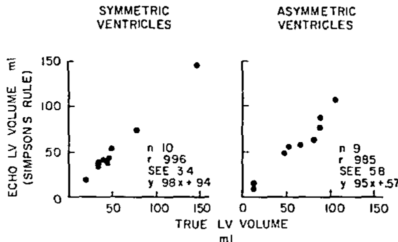


Fig 5 Comparison of volume in formalin fixed left ventricles, cross-sectional echocardiography (Simpson s rule Model 1) on the Y axis versus true volume on the X axis A linear regression analysis was performed for calculated versus true volume the regression equation is shown The correlation coefficients were excellent for both symmetric (n = 10) and asymmetric (n = 9) ventricles, 0 996 and 0 985 respectively N = number of ventricles r = correlation coefficient SEE = standard error of estimate

cles LV volume calculated by the above five models was compared to true fluid volume of the LV Linear regression analysis was performed and standard error of estimate was calculated Per cent error was determined as follows

$$\text{percent error} = \frac{\text{calculated LV volume} - \text{true LV volume} \times 100}{\text{true LV volume}}$$

For each of the five models calculated LV volume was plotted against true LV volume Percent errors were plotted and mean percent error was calculated as an average of absolute percent errors for the 10 symmetric and nine asymmetric left ventricles

Results

For 10 symmetric hearts the mean ratio of septal lateral diameter to anterior posterior di ameter was 1 23 ± 0 06 (mean ± SEM) and vol ume ranged from 19 5 to 146 milliliters For nine asymmetric hearts the mean ratio was 1 80 ± 0 07 and volume ranged from 13 0 to 105 5 milliliters

Results of both linear regression and percent error analyses are summarized in Table I for all five mathematic models Correlation coefficients and mean percent error are listed for a compari son between echo volume and true volume of the formalin fixed left ventricle The results of testing mathematic models 1 and 5 are graphically illus trated in Figs 5 and 6 Points are plotted for calculated volume versus fluid volume for 10 symmetric ventricles and for nine asymmetric ventricles the regression equation correlation coefficient standard error of estimate and mean percent error are listed for each model. With symmetric ventricles excellent correlations were obtained for all mathematic models correlation coefficients ranged from 0 996 to 0.967 and mean percent error ranged from 5 9% to 30 9% Although reductions in r value with asymmetric ventricles were statistically significant for all five models only in Models 4 and 5 did r values decline below 0 95

Fig 5 shows a comparison between echo vol ume by the Simpson s rule (Model 1) on the Y axis and true volume on the X axis The correla tion coefficients were excellent for both symmet ric and asymmetric ventricles 0 996 and 0 980 respectively Mean percent errors were low for both groups 5 9% to 9.8% respectively

With Model 2 (Table I) the short axis area length method correlation coefficients were excellent for both symmetric and asymmetric ventricles 0 993 and 0.974 respectively mean percent errors for Model 2 were low 10 1% and 20 3% respectively These values did not differ

lumen toward the base of the LV Since the internal cavity structure of the formalin fixed left ventricle was not precisely the same as that of the normal left ventricle the regression equation for each mathematic model may not be appropriate for application to the left ventricular volume in the beating heart Nevertheless the formalin fixed left ventricle is quite useful in evaluation of the relative merits of mathematic models for quantification of left ventricular volume For Model 1 in particular our results indicate that no regression equation is necessary in either symmetric or asymmetric ventricles this is evident from the fact that the regression slopes (m) are very close to 1 0 and regression intercepts (I) are very close to zero (Table I)

In summary this in vitro study of cross sectional echocardiography has demonstrated that volume of the symmetric left ventricle may be quantified reliably with all mathematical models tested but volume of the asymmetric left ventricle is quantified most reliably by models that incorporate left ventricular length and either short axis area or two short axis diameters

Summary

Cross sectional echocardiography was utilized for quantification of volume in 19 formalin fixed left ventricles in the presence or absence of ventricular symmetry, defined by the ratio of septal lateral to anterior posterior diameter In 10 symmetric ventricles this ratio was 1 23 ± 0 06 (mean ± SEM) whereas in nine asymmetric ventricles the ratio was 1 80 ± 0 07 Area diameter and length measurements were obtained from short and long axis cross sectional images of the left ventricle and volume was calculated by five mathematical models previously described To evaluate the reliability of each model echocardiographic left ventricular volume was compared by linear regression and percent error analyses to directly measured fluid volume

In symmetric ventricles excellent correlations (r = 0 996 to 0 967) and reasonable mean percent errors (6% to 31%) were observed for all models In asymmetric ventricles models utilizing short axis area or two short axis diameters retained high correlation coefficients (r = 0 985 to 0 9?6) and similar mean percent errors but standard formulas previously used with M mode echo and angiography showed lower correlations (r = 0.8?? to 0 873) and higher mean percent errors (?% to 54%) Thus, in the presence of ventricular asymmetry analysis of short axis areas or diameters with cross sectional echocardiography is well suited for quantification of left ventricular volumes

We gratefully acknowledge the technical assistance of Olga Diner We also thank Barbara Voigt and Jeanne Bloom for their assistance in the preparation of this manuscript.

REFERENCES

1 Pombo J F Troy B L and Russel, R. A, Jr Left ventricular volumes and ejection fraction by echocardiography Circulation 43 480 1971
2 Fortuin N J Hood, W P Jr Sherman M E, and Craige E Determination of left ventricular volumes by ultrasound Circulation 44 575 1971
3 Feigenbaum H Popp R L Wolfe S B Troy B L, Pombo F J Haine C L and Dodge H T Ultrasound measurements of left ventricle A correlative study with angiography Arch Intern Med 129 461 1972
4 Teichholz L F Kreulen, T., Herman M V and Gorlin R Problems in echocardiographic volume determinations Echocardiographic angiographic correlations in the presence or absence of asynergy Am J Cardiol 37 1976
5 Feigenbaum H Echocardiographic examination of the left ventricle Circulation 51 1 1975
6 Linhart J W Mintz, G S Segal, B L Kawai N and Kotler M N Left ventricular volume measurement by echocardiography Fact or fiction? Am J Cardiol 36 114 1975
7 Wyatt H L Heng M K Meerbaum S Hestenes J D Cobo J M Davidson R M and Corday E Cross sectional echocardiography I Analysis of mathematic models for quantifying mass of the left ventricle in dogs Circulation 60 1104 1979
8 Wyatt H L Heng M K Meerbaum S Gueret P Dula E and Corday F Cross-sectional echocardiography II Analysis of mathematic models for quantifying volume of the formalin fixed left ventricle Circulation 61 1119 1980

ymmetric ventricles and a substantially higher 32.1% for asymmetric ventricles

Fig 6 shows a comparison between echo volume by the cube method (Model 5) on the Y axis and the true volume on the X axis The correlation coefficient was very good for symmetric ventricles r = 0.967 in contrast the correlation coefficient was substantially lower for asymmetric ventricles r = 0 873 Mean percent error was substantially higher for asymmetric ventricles (53.5% versus 29 8%) than for symmetric ventricles

Discussion

This study of cross sectional echocardiography demonstrates that volume can be accurately quantified in asymmetric as well as symmetric left ventricles using either short axis areas (Models 1 and 2) or two short axis diameters (Model 3) and ventricular length Mathematical models of the present study were developed and tested in previous studies from this laboratory quantifying mass of the left ventricle in anesthetized dogs and volume in formalin fixed left ventricles [7, 8] Models 1 and 2 utilizing short axis area and length of the left ventricle were developed specifically for cross sectional echocardiography These models proved to be the most reliable for volume and mass quantification of the left ventricle [8] by virtue of the high correlation coefficients low mean percent errors and even distribution of regression points about the line of identity The fact that Model 2 proved statistically to be just as reliable as Model 1 in the present study as well as in the LV mass study[7] emphasizes the practical importance of the simple formula $V = 5/6\,AL$ in both experimental and clinical application Interestingly for asymmetric ventricles of the present study Model 3 ($V = \pi/6\, D_1 D_2 L$) proved statistically to be just as adequate as Model 2 for LV volume quantification

Model 4 the long axis area length method normally used with angiography and Model 5 the cube method used with M mode echocardiography were quite reliable for quantification of volume in symmetric ventricles but much less reliable in the presence of ventricular asymmetry These findings of the present study are in general agreement with the findings of previous clinical studies of left ventricular volumes In patients with symmetric myocardial wall motion [1-4] good correlations were demonstrated between M mode echocardiography and angiography but in patients with regional myocardial asynergy poor correlations were encountered [6] indicating that estimation of asymmetric volumes from a single M mode echo dimension is unreliable These observations reveal the major underlying assumption of Models 4 and 5 namely that the endocardial surface must be sufficiently symmetrical to be described as an ellipsoid Because the manifestation of ventricular asymmetry due to myocardial ischemia or infarction is usually apparent only during the systolic phase of the cardiac cycle the major error in volume quantification occurs during systole

Clinical application of these cross sectional echocardiographic mathematic models is dependent on the quality of short axis cross sectional images available in the human If endocardial definition is adequate Models 1 2 or 3 may account for the presence of ventricular asymmetry in the computation of left ventricular volume Since it is difficult in patients to obtain adequate short axis images at more than one or two levels of the left ventricle Models 2 and 3 will probably be most applicable in the clinical situation The ventricular asymmetry simulated in this study was a minor axis asymmetry generally consistent for the entire length of the left ventricle thus Models 2 and 3 utilizing measurements from only one minor axis section gave results only slightly less reliable than Model 1 Since dyssynergy due to regional myocardial ischemia or aneurysm may not extend the entire length of the left ventricle but may instead be localized (for instance to the apical half of the ventricle) Models 2 and 3 might tend to be less reliable than Model 1 unless the volume computations incorporate measurements from a minor axis section within the dyssynergic region Thus the particular type of ventricular asymmetry used in this study may not have a specific clinical or physiologic analogy but the results of this study may nevertheless have general implications for volume quantification in the presence of ischemia infarction aneurysm or asymmetric hypertrophy

The effects of formalin fixation procedures in the present study were reflected in minor changes of ventricular chamber characteristics (1) some loss of prominence of papillary muscle projections into the ventricular cavity (2) a smoothing effect on rough edges of the endocardial surface (trabeculae carneae) and (3) a constriction of the cavity

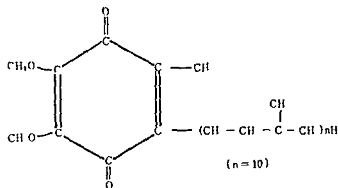


Fig 1 Chemical structure of coenzyme Q

Table I Chemical contents (w/w) in fatty acid emulsion

Linolenic acid	0 77%
Linoleic acid	5 16%
Oleic acid	2 40%
Stearic acid	0 44%
Palmitic acid	1 24%
Egg yolk	1.20%
Glycerin	2 50%

The chemical structure of coenzyme Q_{10} is shown in Fig 1 Half of each group was observed for 40 minutes after the reperfusion of the preceding occlusion

The method of the measurement of VMRT was described in detail previously [1] In brief a series of rectangular pulses (100 Hz 1 msec in duration) were given throughout the ventricular vulnerable period with the electrode attached to a potential ly nonischemic area of the left ventricle The intensity of pulses was increased gradually until more than five extrasystoles occurred successive ly to obtain VMRT In order to measure mito chondrial function it is necessary to avoid the myocardial injury induced by any artifact such as regional burn by DC countershock In many cases less than 10 successive ventricular extr isys toles did not lead to ventricular fibrillation and when the electrical stimulus was stopped cardiac rhythm returned to normal without DC counter shock Therefore we use VMRT instead of ven tricular fibrillation threshold (VFT) as an index of arrhythmogenicity Although VMRT was less than VFT good reproducibilit of this method was observed

Venous blood was taken from the femoral vein and blood pH serum elc tr lytes Na K Ca

Table II Indices of mitochondrial funct [illegible] 15 minute occlusion groups

Groups	Saline + 15 min occ (n = 6)	Fatty acid + 15 min occ (n 5)
N		
RCI	4.25 ± 0.2[illegible]	40[illegible] 0.3[illegible]
ADP/O	1 99 ± 0 0[illegible]	1 9[illegible] 0 04
ATP	582 ± [illegible]9 7	504 [illegible]9
I		
RCI	3 34 ± 0 25	2.51 0.[illegible]
ADP/O	1 9[illegible] ± 0 05	n.d.
ATP	468 ± 48 6	n.c.

(Mean ± SD)
nmoles/mg protein/minut
N nonischemic area I ischemic area n d not d tectable n c not calculated

and Cl were measured Throughout the exp ment Lead II of the ECG was monitored

Canine hearts of another half of each gro were isolated immediately after 15 or 30-minute occlusion and myocardial mitochondria were prepared according to Hatefi s method In order to measure the respiratory control index (RCI and ADP/O of the myocardial mitochondria 2 ml of mannitol reaction mixture (0 3 M man tol 10 mM phosphate 2 5 mM MgCl 10 mM KCl and 0 25 mM EDTA pH 7 4) and 0 3 ml of the mitochondrial sample (10 mg mitochondrial protein per milliliter) were added together with 0 1 ml of potassium succinate (0 2 M) a d 0 ml or 0 03 ml of ADP (0 01 M) as substrates to reaction cell mounted with the oxygen electrode (Kyusui Kagaku Ltd)

ATP production rate (nmoles/mg mitoch drial protein/minute) was calculated as ADP O × oxygen consumption rate in State III mitochondrial protein/minute

Results

In Fig 2 the time courses in VMRT in the 15 minute occlusion groups are shown In the saline infused group the initial mean val e of 1 59 ± 0 09 mA (mean ± SE) was significan decreased to 1 13 ± 0 08 mA 1 07 ± 0 08 mA at 7 5 and 15 minutes after ligation respectively Reduced VMRT 1 18 ± 0 07 mA was observed at 10 minutes after the release of ligation howev er at 20 minutes after the release VMRT

Recovery time course of ventricular vulnerability after coronary reperfusion in relation to mitochondrial function in ischemic myocardium

Satoru Sugiyama, M.D.*
Takayuki Ozawa, M.D.*
Tadayuki Kato, M.D.**
Shohachi Suzuki, M.D.*
Nagoya, Japan

Although in 1935 Tennant and Wiggers noted a high incidence of ventricular arrhythmias (reperfusion arrhythmias) after the sudden restoration of blood flow to an occluded coronary artery in canine experiments, and similar findings have been observed by other investigators, reperfusion arrhythmias remain less familiar than the arrhythmias seen during acute coronary occlusion. However, with the advent of coronary bypass surgery and with advances in coronary angiography indicating the relationship between coronary artery spasm and Prinzmetal's angina, the subjects of ventricular arrhythmias and ventricular vulnerability to fibrillation following the release of a previously ligated coronary artery have attracted much interest and have been extensively studied in recent years. Nevertheless, the mechanism whereby ventricular fibrillation is precipitated during reperfusion of ischemic myocardium remains uncertain.

We have studied the time courses in ventricular multiple response threshold (VMRT) during coronary occlusion and after release of occlusion and have suggested that the recovery time course in VMRT closely relates to recovery of heart mitochondrial function following coronary reperfusion.

In this study, the effects of the duration of occlusion time and infusion of fatty acid emulsion or infusion of coenzyme Q on myocardial mitochondrial function were investigated in relation to the recovery time courses in VMRT following coronary reperfusion.

Methods

Forty-eight mongrel dogs of both sexes and weighing between 10 and 15 kg were anesthetized with sodium pentobarbital (30 mg/kg) intraperitoneally. Under artificial respiration, the chest was opened in the fourth or fifth intercostal space and the heart was suspended in a pericardial cradle. A silk ligature was placed at the proximal branch of the left anterior descending coronary artery.

The dogs were divided into four groups (12 dogs each) according to the duration of coronary occlusion time and infusion of drugs.

Group 1. 15 minute occlusion after saline infusion.

Group 2. 15 minute occlusion after free fatty acid emulsion (contents are shown in Table I) ml/kg infusion.

Group 3. 30 minute occlusion after saline infusion.

Group 4. 30 minute occlusion after coenzyme Q 5 mg/kg infusion.

From the Department of Biomedical Chemistry, Faculty of Medicine, University of Nagoya, and the Third Department of Internal Medicine, Faculty of Medicine, University of Nagoya, Nagoya, Japan.

Received for publication July 17, 1979.
Accepted for publication Nov. 9, 1979.

Reprint requests: Dr. Satoru Sugiyama, Dept. of Biomedical Chemistry, Faculty of Medicine, University of Nagoya, Tsurumai-cho, Showa-ku, Nagoya 466, Japan.
*Dept. of Biomedical Chemistry, Faculty of Medicine, University of Nagoya.
**Third Department of Internal Medicine, Faculty of Medicine, University of Nagoya.

0002-8703/80/120829 + 09$00.90/0 © 1980 The C. V. Mosby Co.

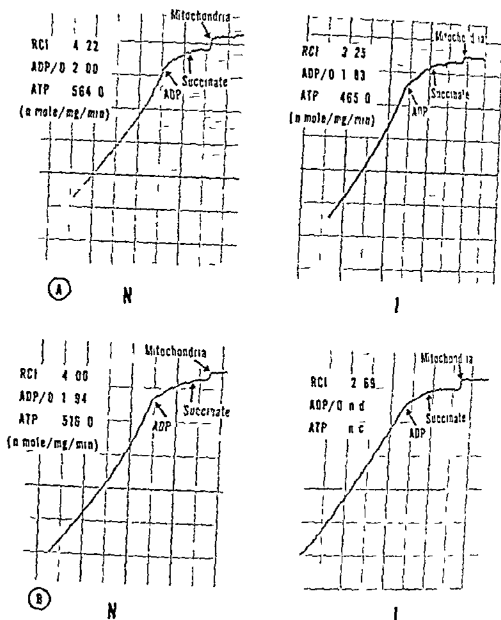


Fig 3 A and B Representative traces of mitochondrial respiration in the saline + 15 minute occlusion group (A) and in the fatty acids + 15 minute occlusion group (B) Infusion of fatty acids accelerated dysfunction of the mitochondria in the ischemic area

The reduced value at 30 minutes was lowered significantly less than that in the saline infused group At 10 and 20 minutes after reperfusion reduced VMRT 1 20 ± 0 07 mA and 1 38 ± 0 05 mA was observed respectively However decrease in VMRT was less remarkable than that of the saline infused group VMRT at 30 minutes after the release of ligation recovered to a value which is not significantly different from the preligation value

These results showed us that it took 40 minutes after reperfusion in the saline infused group and 30 minutes in the coenz me Q infused group to recover the value of VMRT to that before ligation respectively

Concerning the heart rate blood pH and serum levels of Na K Ca Cl no significant changes were detected between the two groups

Table III represents mitochondrial indices of 30 minute occlusion groups As shown in the Table mitochondria isolated from an ischemic area showed significantly lowered indices compared with those of nonischemic mitochondria By 30 minute occlusion ischemic mitochondria of the saline infused group showed further lowered [illegible] those of the

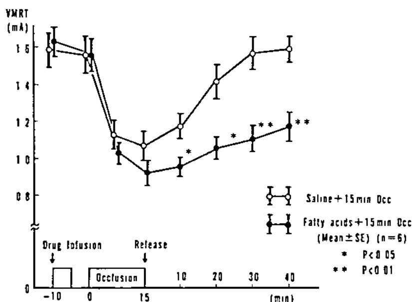


Fig 2 Time courses in VMRT of the 15-minute occlusion group In the fatty acid infused group the recovery time course of VMRT was significantly retarded

returned to a value which is not significantly different from that before ligation

In the fatty acids-infused group the initial value of 1 63 ± 0 08 mA was not significantly decreased by fatty acid infusion itself After ligation VMRT decreased significantly to 1 03 ± 0 06 mA at 7.5 minutes after ligation and to 0 92 ± 0 07 mA at 15 minutes after ligation The reduced VMRT persisted i e 0 96 ± 0 05 mA 1 06 ± 0 06 mA 1 11 ± 0 07 mA and 1 18 ± 0 08 mA at 10 20 30 and 40 minutes after the release of ligation respectively These reduced values were significantly lower than those of the saline infused group

These results showed us that it took 20 minutes in the saline infused group and over 40 minutes in the fatty acid-infused group respectively to restore the value of VMRT to that before ligation

Concerning the heart rate blood pH and serum levels of Na K Ca Cl no significant changes were detected in the two groups

Indices of mitochondrial function (RCI ADP/O ATP production rate) are shown in Table II In both groups mitochondria isolated from an ischemic area showed significantly lowered RCI comparing with that of mitochondria isolated from a nonischemic area It was noted that mitochondria isolated from an ischemic area of the fatty acid-infused group showed significantly lowered indices compared with those of ischemic mitochondria of the saline infused group Ischemic mitochondria of the fatty acid-infused group showed no reestablishment of the controlled respiration after the addition of ADP (Fig 3) i e by ischemia and more by fatty acid infusion myocardial mitochondria became loosely coupled showing little or no dependence of respiratory rate on ADP Thus ADP/O and ATP production rate could not be calculated

In Fig 4 the time courses in VMRT in the two 30 minute occlusion groups are shown In the saline infused group the initial value of VMRT 1 56 ± 0 09 mA was decreased to 1 20 ± 0 07 mA 1 06 ± 0 06 mA and 0 99 ± 0 05 mA at 10 20 and 30 minutes after the ligation respectively Reduced VMRT 1 02 ± 0 07 mA 1 10 ± 0 08 mA and 1 23 ± 0 08 mA was observed at 10 20 and 30 minutes after the release of ligation respectively while VMRT measured at 40 minutes after the release of ligation recovered to a value which is not significantly different from the preligation value In the group infused with coenzyme Q (5 mg/kg) the initial value of 1 62 ± 0 07 mA was decreased to 1 21 ± 0 05 mA 1 24 ± 0 05 mA and 1 21 ± 0 05 mA at 10 20 and 30 minutes after ligation respectively

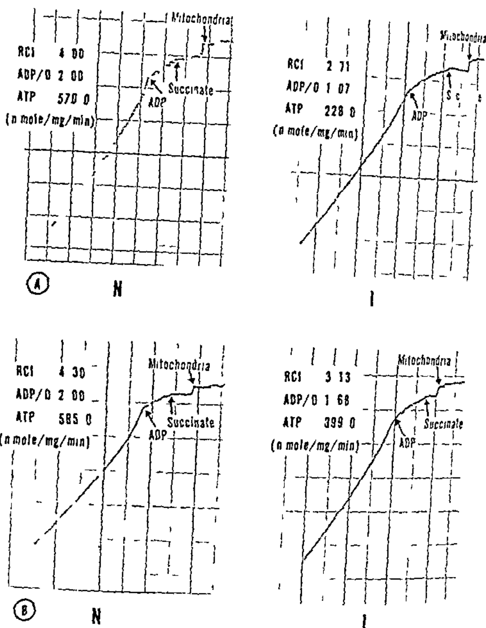


Fig 5 A and B Representative traces of mitochondrial respiration in the saline + 30 minute occlusion group *(A)* and in the coenzyme Q + 30 minute occlusion group *(B)* Coenzyme Q infusion prevented mitochondrial dysfunction induced by 30 minutes of ischemia

chondrial membrane and the mitochondria to be loosely coupled Coenzyme Q, isolated first by Crane and colleagues is an important factor of the mitochondrial electron transfer system as shown in Fig 7 Coenzyme Q transfers electrons from Complex I or II to Complex III In the mitochondria obtained from the ischemic area the electron transfer activity between Complex I and III was reduced and the mitochondrial dysfunction induced by ischemia might be derived partly from this electron transfer disturbance Administration of coenzyme Q preserved even if not completely the activity of the electron transfer system and resulted in better mitochondrial function compared with controls (Table III)

It is interesting that the recovery time course of VMRT of the saline + 15 minute occlusion group was similar to that of the coenzyme Q + 30 minute occlusion group The recovery time course in VMRT of the fatty acid emulsion + 15 minute occlusion group was also similar to that of the saline + 30 minute occlusion group These relationships of the two groups were also apparent in mitochondrial damage In other words, the

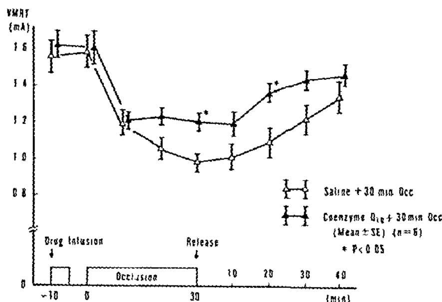


Fig. 4. Time courses in VMRT of the 30-minute occlusion group. In the coenzyme Q-infused group recovery of VMRT was significantly shortened compared to that of the saline infused group.

minute occlusion group (Tables II and III). However these indices were significantly preserved by the administration of coenzyme Q.

Fig. 5 shows representative traces of mitochondrial respiration in these two groups. It was also confirmed that the administration of coenzyme Q prevented mitochondrial dysfunction caused by ischemia.

Discussion

We have reported[13] that VMRT which was lowered during coronary occlusion recovered in the course of time after the release of ligation and that the recovery time course in VMRT depended upon the duration of the preceding occlusion time. But it remains obscure which factor truly affects the recovery time course in VMRT.

Our previous report showed that the administration of fatty acid emulsion of 1 ml/kg did not cause mitochondrial dysfunction in the well oxygenated heart but accelerated the mitochondrial dysfunction induced by ischemia. The report also showed that the infusion of fatty acids delayed the recovery of VMRT. According to these results we have suggested that mitochondrial function is one of the important determining factors of the recovery time course in VMRT.

As summarized in Fig. 6 and Table IV this experiment revealed that (1) the longer the duration of occlusion time the longer was the necessary recovery time in VMRT, (2) the longer the duration of occlusion time the more severe was the mitochondrial damage caused, (3) fatty acid infusion accelerated mitochondrial damage induced by ischemia and coenzyme Q_{10} administration prevented the mitochondrial damage, and (4) the recovery time in VMRT was in parallel with mitochondrial damage. As for mitochondrial function, myocardial ischemia suppressed the activity of the mitochondrial electron transfer system and β oxidation cycle of fatty acids because of the accumulation of acyl CoA which inhibits the ADP ATP exchange reaction of mito

Table III. Indices of mitochondrial function in 30 minute occlusion groups

Groups	Saline + 30 min occ (n = 6)	Coenzyme Q + 30 min occ (n = 6)
N		
RCI	4.15 ± 0.25	4.24 ± 0.19
ADP/O	1.96 ± 0.04	1.90 ± 0.09
ATP	564 ± 35.1	549 ± 43.5
I		
RCI	2.50 ± 0.38	3.28 ± 0.22
ADP/O	1.22 ± 0.34	1.69 ± 0.18
ATP	243 ± 90.3	402 ± 51.3

(Mean ± S.D.)
nmoles/mg protein/min
N nonischemic area. I ischemic area

Table IV Indices of mitochondrial function in all four groups

	Mitochondria obtained from ischemic area		
	RCI	ADP/O	ATP*
Saline + 15 min occ	3.34 ± 0.25	1.9? ± 0.05	469 ± 49.5
Coenzyme Q_{10} + 30 min occ	3.?8 ± 0.2?	1.69 ± 0.18	40? ± 31.3
Saline + 30 min. occ	2.50 ± 0.38	1.2? ± 0.34	?43 ± ?3
Fatty acids + 15 min occ	2.51 ± 0.36	n.d.	n.c.

(Mean ± S.D.)
*nmoles/mg protein/minute
n.d. not detectable n.c. not calculated

severe the mitochondrial damage the longer was the necessary recovery time in VMRT.

Any proposals as to possible mechanisms for the observed results must be highly speculative. However if the depletion of cytosolic ATP which is produced mainly by mitochondria shortened the action potential duration as Cowan and Vaughan Williams reported the shortened duration of the action potential could be responsible for reentry in ventricular muscle and ventricular fibrillation. Therefore it is possible that mitochondrial function i.e. the rate of ATP supply is one of the important determining factors in the recovery time courses in VMRT.

Summary

This experiment was designed to investigate the effect of the duration of occlusion time and the infusion of fatty acid emulsion or that of coenzyme Q on myocardial mitochondrial function and on the recovery time course in VMRT following coronary reperfusion. Forty eight anesthetized mongrel dogs were divided into four groups based on the duration of the occlusion time and the infused drug. Group 1 was the saline + 15 minute occlusion group. Group 2 was the fatty acid emulsion (1 ml/kg) + 15 minute occlusion group. Group 3 was the saline + 30 minute occlusion group and Group 4 was the coenzyme Q (5 mg/kg) + 30 minute occlusion group. After the drug administration (saline, fatty acid emulsion or coenzyme Q) the left anterior descending coronary artery was ligated for 15 or 30 minutes. In one half of each group canine hearts were isolated immediately at 15 or 30 minutes after ligation to prepare myoc[illegible] mitochondria. In the other half of each gr[illegible] the ligation was released and coronary flow w[illegible] reperfused. VMRT was measured before d[illegible] and after the ligation. The recovery time course [illegible] the saline + 15 minute occlusion group was simi[illegible] lar to that of the coenzyme Q_{10} + 30-minute occlusion group and the recovery time co[illegible] the fatty acid + 15 minute occlusion group was similar to that of the saline + 30 minute occlu[illegible] sion group. This relationship of the two group[illegible] was recognized in the mitochondrial dama[illegible] suggested that mitochondrial damage in oth[illegible] words energy supply dysfunction is one of the determining factors of recovery in VMRT af[illegible] coronary reperfusion.

REFERENCES

1 Tennant R and Wiggers C J The effect of coron[illegible] occlusion on myocardial contraction Am J Ph[illegible] 112 351 1935
2 Harris A S and Rojas A G The initiation of ve[illegible] ular fibrillation due to coronary occlusion Exp M[illegible] Surg 1 105 1943
3 Harris A S Estandia A and Tillotson R F [illegible] ular ectopic rhythms and ventricular fibrillation [illegible] ing cardiac sympathectomy and coronary occlusion [illegible] J Physiol 165 505 1951
4 Sewell W H Koth D R and Huggin C E [illegible] ular fibrillation in dogs after sudden return of [illegible] coronary artery Surgery 38 1050 1955
5 Oliva P B Potts D E and Pluss R G Coro[illegible] arterial spasm in Prinzmetal's angina N Engl J M[illegible] 288 745 1973
6 Lang T W Corday E Gold H Meerbaum S R[illegible] Lang T W Corday E Gold H Meerbaum S and Rosen [illegible] S Constantini C Hirose S Osher J and P[illegible] Consequences of reperfusion after coronary occl[illegible] Am J Cardiol 33 69 1974
7 Battle W E Naimi S Avitall B Brilla A H [illegible] J S Jr Bete J M and Levine H J Di[illegible]

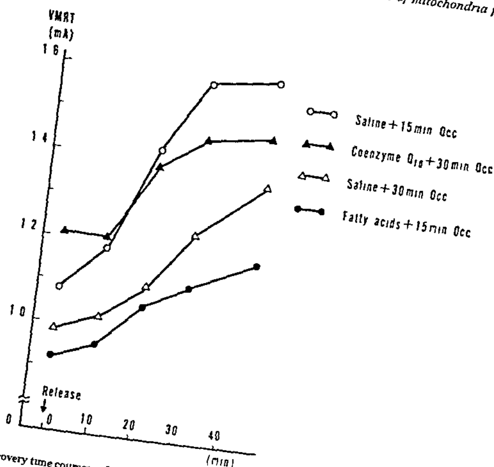


Fig 6 Recovery time courses in VMRT of all four groups Recovery time course in the VMRT of the saline + 15-minute occlusion group was similar to that of the coenzyme Q + 30-minute occlusion group and that of the saline + 30-minute occlusion group was similar to that of the fatty acid + 15 minute occlusion group

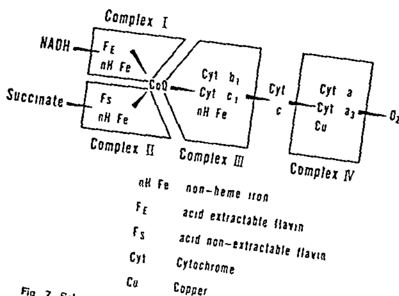


Fig 7 Schema of the mitochondrial electron transfer system

An electrocardiographic—pathologic correlative study on left axis deviation in hypertensive hearts

Tatsuji Takagi M D *
Ryozo Okada, M D **
Tokyo Japan

Left axis deviation (LAD) has been generally ascribed to left anterior hemiblock (LAH)[1] or left anterior focal block [4] While some investigators have attempted to find a correlation between LAD and LAH questions such as whether LAD is in fact consistent with LAH whether LAH is specific for LAD and what degree of LAD indicates LAH remain to be answered Therefore we carried out a study to correlate LAD and conduction system pathology in autopsied hypertensive hearts with special reference to the left bundle branch (LBB)

Materials and methods

The well preserved hearts of 35 arterial hypertension patients (18 males 17 females, ranging in age from 38 to 89 years) autopsied between 1970 and 1976 were studied and compared pathologically Only specimens from essential (EH) and renal hypertension (RH) cases and cases with hypertension complicating aortic insufficiency (AI) are included in this study The patients whose electrocardiograms (ECGs) showed left bundle branch block (LBBB) or myocardial infarction were excluded

The materials were divided into three groups based on mean QRS axis calculated by the triaxial reference system in the frontal plane Group 1 consisted of seven EH, three RH, and two AI cases with left axis deviation of −89 degrees to −30 degrees In Group 2 there were eight EH two RH and one AI with semi left axis deviation of −29 degrees to 0 degrees Group 3 was comprised of six EH, five RH and one AI with normal axis deviation of 1 degree to 89 degrees

After gross examination of the hearts, left ventricular volume was calculated according to the method of Lev and associates [5]

For histological examination of the atrioventricular conduction system step sections were prepared according to a modification of the method of Lev and co-workers In addition to the regular four blocks, three further blocks were obtained—i e , one block each of the peripheral portions of the left anterior and posterior radiation (LBB and LBB, respectively) and one block from the apex including the left and right ventricle and interventricular septum From each block five 7 micron thick slices were cut stained with hematoxylin eosin (HE) periodic acid Schiff (PAS), and Elastica van Gieson (EvG) method and observed under a light microscope If necessary additional histologic sections were used

Results

The ages and sex distribution of the patients QRS axes cardiac weights, and left ventricular measurements are shown in Table I Except for the QRS axes there were no significant differences among the three groups Incidence of LVH by ECG using criteria of Sokolow and Lyon was 58% in Group 1 73% in Group 2 and 83% in Group 3

To compare severity of the lesions in the conduction system four categories ranging from absent to severe were established (Table II) L

From Yokosuka Kyosai Hospital Department of Internal Medicine Yokosuka Japan

Received for publication on July 30 1979
Accepted for publication on Oct 16 1979

Reprint requests Dr Tatsuji Takagi Dept of Internal Medicine Metropolitan Bokuto Hospital 1 4 1 Kotobashi Sumida ku Tokyo 130 Japan.

* Dept. of Internal Medicine Metropolitan Bokuto Hospital
** Dept. of Internal Medicine Juntendo University School of Medicine Juntendo University

course of ventricular vulnerability to fibrillation during and after release of coronary ligation Am J Cardiol 34 4? 19 4
Axelrod P J Verrier R L and Lown B Vulnerability to ventricular fibrillation during acute coronary arterial occlusion and release Am J Cardiol 36 ""6 19 5
9 Levites R Banka V S and Helfant R H Electrophysiologic effects of coronary occlusion and reperfusion Circulation 52 60 1975
0 Corbalan R Verrier R L and Lown B Differing mechanisms for ventricular vulnerability during coronary artery occlusion and release AM HEART J 92 ? 3 19 6
1 Blatt C M Verrier R L and Lown B Acute blood pressure elevation and ventricular fibrillation threshold during coronary occlusion and reperfusion in the dog Am J Cardiol 39 523 19/7
? Stockman M B Verrier R L and Lown B Effect of nitroglycerin on vulnerability to ventricular fibrillation during myocardial ischemia and reperfusion Am J Cardiol 43 ?33 19 9
3 Suzuki, S Kato T Kambe T Sakamoto N Sugiyama S and Ozawa T An experimental study of release arrhythmia Occlusion time dependent changes in ventricular fibrillation threshold AM HEART J 98 19/9
4 Kato T Suzuki S Kambe T Sakamoto N Sugiyama S and Ozawa T Arrhythmogenicity of free fatty acids in relation to heart mitochondrial function J Appl Biochem 1 139 19"9
15 Bigger J T Jr Dresdale R J Heissenbuttel R H Weld F M and Wit A I Ventricular arrhythmias in ischemic heart disease Mechanism prevalence significance and management Prog Cardiovasc Dis 19 255 19
16 Okuma K Sugiyama S Wada M Sugenoya J Nimi N Oguri H Toyama J and Yamada K Experimental studies on the anti arrhythmic action of a lidocaine analog Cardiology 61 ?89 19 6
17 Hatefi Y Jurtshuk P and Haavik A G Studies on the electron transport system XXXII Respiratory control in beef heart mitochondria Arch. Biophys. Biochem 94 148 1961
18 Crane F L Hatefi Y Lester R L and Widmer C Isolation of a quinone from beef heart mitochondria Biochem Biophys Acta 25 ?20 1957
19 Sugiyama S and Ozawa T Activity of Coenzyme Q in ischemic mitochondria J Appl. Biochem (submitted)
0 Cowan J C and Vaughan Williams E M The effects of palmitate on intracellular potential recorded from Langendorff perfused guinea pig hearts in normoxia and hypoxia and during perfusion at reduced rate of flow J Molec Cell Cardiol 9 3?/ 19/7

r

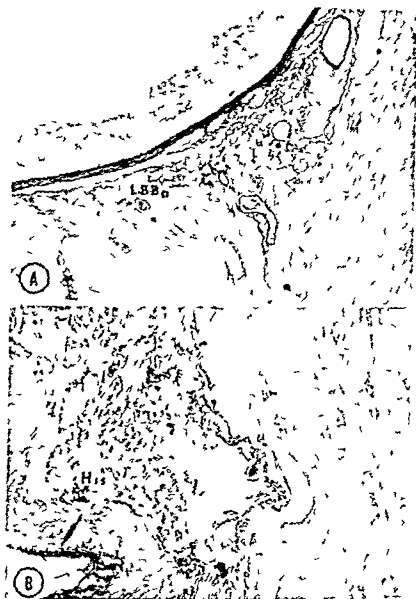


Fig 1 *A* A 40-year old male with fibrosis and fatty degeneration of the peripheral portion of the LBB (Elastica Van Gieson stain original magnification ×40) *B* An 85 year old male with fibrosis of the His bundle (His) (Elastica Van Gieson stain original magnification ×40) Both specimens are from Group 1

cells were intact at LBB_p (Fig 4C) These findings were consistent with LAD

Case 3 A 58 year old male presented with aortic insufficiency and hypertension He died of congestive heart failure The ECG initially revealed the QRS axis to be −9 degrees (Fig 5*A*) at a later time the axis was noted to have shifted to the left and finally the axis was −30 degrees with junctional rhythm and slight widening of the QRS (Fig 5*B*) Histology revealed marked reduction of the conduction cells at LBB and LBB_p due to entrapment by thickened subendocardial fibrous tissue (Fig 5C D E and F)

Case 4 A 43 year old female presented with chronic renal failure (RH) While the QRS axis was normal at 43 degrees (Fig 6A) both anterior and posterior radiations of the LBB were damaged by marked fibrosis and fatty infiltration (Fig 6*B* and *C*)

Discussion

1 Extent of LAD in LAH To our knowledge no genuine studies on the correlation between the electrocardiographic and pathologic findings have been published and there is no consensus regarding the extent of LAD which is compatible with LAH

Demoulin and Kulbertus reported a correla-

Table I Comparison of the three groups based on QRS axis and gross pathological findings

Group	No of cases	Sex		Age (years)	Electrical axis (°)	Cardiac weight (g)	Left ventricle	
		M	F				Thickness (mm)	Volume (mL)
1	12	6	6	65.4 ± 14.8	−40.1 ± 8.9	441 ± 1[illegible]6	13.4 ± 3.1	21.8 ± 19.1
2	11	6	5	69.3 ± 4.[illegible]	−16.4 ± 6.2	399 ± [illegible]6	14.4 ± 2.1	14.2 ± 6.5
3	12	6	6	6[illegible].0 ± 14.9	46.3 ± 18.6	447 ± 11[illegible]	14.1 ± 1.9	19.6 ± 12.[illegible]

(Mean ± standard deviation)

Table II Severity of the lesions in the conduction system

Group	His bundle				LBB				LBB			
	0	+	++	+++	0	+	++	+++	0	+	++	+++
1	6	4	0	2	2	5	4	1	0	2	1	9
2	5	2	4	0	2	6	1	2	3	4	2	2
3	7	4	1	0	4	4	1	3	1	6	2	3

LBB = left bundle branch (p posterior, a anterior)
Degree of severity 0 normal + mild ++ moderate +++ severe (Severe lesion means reduction of the conduction cells more than 50%)

Table III Histological findings of the conduction system and incidence of severe lesions

Group	His bundle			Posterior radiation (LBB_p)			Anterior radiation (LBB_a)			
	Fibrosis	Calcification	Total	Fibrosis	Degeneration	Total	Fibrosis	Degeneration	Bleeding	Total
1	1	1	2	1	0	1	5	2	2	9
2	0	0	0	1	1	2	1	1	0	2
3	0	0	0	2	1	3	2	1	0	3

This table severe lesion means reduction of conduction cells by more than 50% One of our group Okada[7] based upon his numerous electrocardiographic pathologic correlation studies recognized as empirical evidence that 50% reduction of conduction cells almost always shows some kind of conduction disturbance Therefore we may call severe lesions with over 50% reduction of conduction cells at LBB anatomical LAH

In Group 1 nine of 12 (75%) specimens showed severe lesions at LBB one of these had lesions at both LBB and LBB_p and another one showed severe lesions at the peripheral portion (Fig 1A) There were also two cases with severe lesions at the bifurcation of the His bundle (Fig 1B) the ECG showed right bundle branch block (RBBB) In this group there was one case without severe lesions in the conduction system the electrical axis was −36 degrees In Group 2 there were two cases each with severe lesions at both radiations and in Group 3 there were three similar cases

The incidence and site of severe lesions is shown in Table III In the 35 specimens fibrosis (Fig 2A) at the His bundle LBB or LBB_p was noted in 13 (37%) degeneration was found (Fig 2B) in six (17%) bleeding (Fig 2C) was seen in two (6%) and calcification (Fig 2D) was noted in one (3%) As for the relationship between the type of hypertension and severe lesions fibrosis was noted most frequently in EH (38%) and degeneration in RH (60%)

Case reports

Case 1 An 89 year old female presented with polycystic kidney (RH) and a QRS axis of −45 degrees (Fig 3A) Histology revealed the subendocardial connective tissue to be thickened and to interrupt the conduction cells of LBB almost completely (Fig 3B and C) At the LBB_p there was mild fibrosis at the proximal portion and the conduction cells were hypertrophic

Case 2 A 77 year old female presented with subarachnoid hemorrhage (EH) and a QRS axis of −58 degrees (Fig 4A) Histology revealed massive bleeding at LBB (Fig 4B) and slight bleeding under the subendocardium The conduction

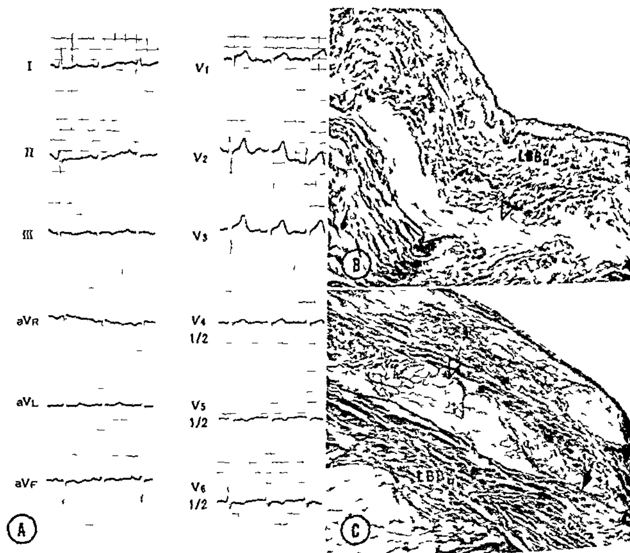


Fig 3 Case I A Electrocardiogram B Proximal portion of the LBB C Somewhat distal portion of the LBB Thick fibrosis *(solid arrows)* interrupts the conduction cells *(open arrows)* (Elastica Van Gieson stain original magnification ×40)

and LAH Although we used the step sectioning (semi serial) method rather than the serial sectioning method our study fulfils the proposed criteria for a genuine correlative study

2 LAD in LAH Conduction delay at LBB is thought to effect LAD in LAH[1 1 1 13] Focal lesions at the His bundle which effect longitudinal dissociation [1] produce LAD and RBBB[16 17] In our series there were two such cases Since the bifurcation of the His bundle can be considered to represent the proximal portion of LBB a block of that portion can be regarded as modified LAH and LAD in LAH can be ascribed to conduction delay at LBB

3 A concept of cancellation In the present series, there were one Group 1 two Group 2 and three Group 3 cases with severe lesions at LBB and LBB_p To answer the questions as to why the spectrum of the mean QRS axis in the frontal plane was so wide despite similar changes at both radiations and why complete LBBB did not occur we propose two hypotheses First conduction disturbances are not always either severe or complete rather in some cases a conduction delay occurs Our second hypothesis is that axis deviation is produced by differences in conduction velocity between the two divisions From these points of view the distribution of the QRS axis summarized as shown in Table IV Only complete conduction block of both divisions yields LBBB and LAD occurs in cases of complete conduction block of LBB or slower conduction at the LB



Fig 2 Histologic findings in severe lesions *A* A 1 year old male from Group 1 with fibrosis at LBB *(solid arrow)* (Elastica Van Gieson stain original magnification ×40) *B* A 38-year-old male from Group 3 with vacuolization and edema at LBB *(solid arrow)* (Elastica Van Gieson stain original magnification ×40) *C* A 60-year old female from Group 1 with bleeding at LBB (Hematoxylin and eosin stain original magnification ×40) *D* An 85 year old male from Group 1 with calcification *(solid arrow)* of the central fibrous body at the His bundle (Elastica Van Gieson stain original magnification ×40) *Open arrows* indicate conduction cells in *A* *B* and *D*

tive study on the conduction system and LAD They found that nine of 10 cases had severe LBB lesions and five of these showed predominant lesions at the anterior subdivision However as their series included some myocardial infarction cases we do not consider theirs a genuine correlative study linking ECG pattern and the conduction system For the same reason we have our reservations about the study reported by Entman and associates

There are two well known criteria in ECG for LAH One is LAD in excess of −45 degrees as postulated by Rosenbaum and co workers and another is LAD in excess of −30 degrees as set down by Kulbertus and colleagues and by Gopal[11] In our series defining severe lesion over 50% reduction of conduction cells at LBB as anatomical LAH and by using the former criteri on sensitivity (true positives/true positives + false negatives) was 25% (four out of 16) and specificity (true negatives/true negatives + false positives) was 100% (19 out of 19) and using the latter criterion sensitivity 69% (11 out of 16) and specificity 95% (18 out of 19) While in the criterion of Rosenbaum and associates specificity was high but sensitivity low we think that the criterion of Kulbertus and associates[10] and of Gopal is more appropriate

We propose that serial sections control materials and relatively uniform specimens from patients without other heart disease such as myocardial infarction or congenital heart disease which may affect the QRS axis should be the criteria for a genuine correlative study on LAD

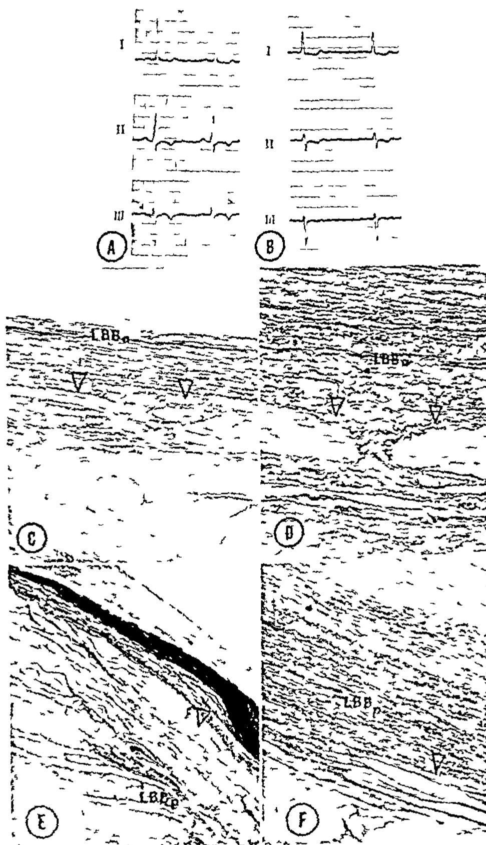


Fig 5 Case 3 *A* Electrocardiogram on Oct 25 1972 *B* Electrocardiogram on July 10 1973 *C* Histologic section shows reduction of conduction cell (Elastica Van Gieson stain original magnification ×40) *D* Thick fibrosis at the LBB (Elastica Van Gieson stain original magnification ×100) *E* Proximal portion of LBB, showing preserved conduction cell (Elastica Van Gieson stain original magnification ×40) *F* Thick fibrosis interrupt the conduction cell of LBB at the distal portion of *E* (Elastica Van Gieson stain original magnification ×40) *Open arrows* indicate conduction cells in *C* to *F*

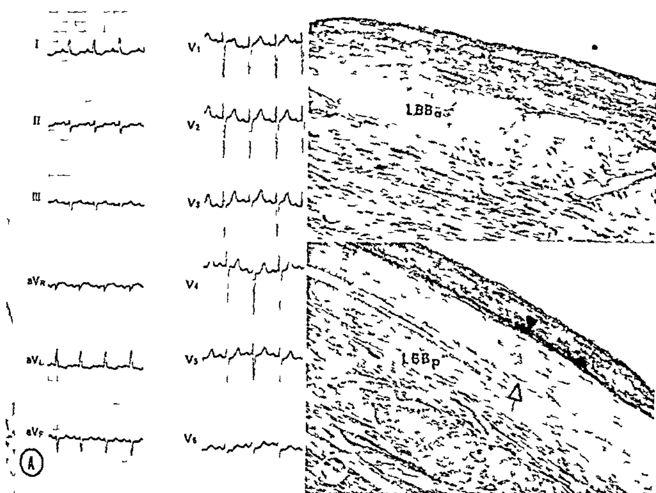


Fig 4 Case 2 *A* Electrocardiogram *B* Massive bleedin at the LBB (Hematoxylin and eosin stain original magnification ×40) *C* Slight bleeding *(solid arrow)* under the subendocardium Conduction cells *(open arrow)* are intact at LBB_p (Elastica Van Gieson stain original magnification ×40)

han at LBB_p In the same conduction delay of oth divisions each cancels the axis deviation of he other (cancellation) In cancellation LBBB loes not occur because of preservation of conduc ion in the LBB although it is slow and the QRS axis remains in the normal range In such cases slight prolongation of the QRS axis may occur

We may explain from our hypotheses that in one of the Group I cases LAD occurred because conduction disturbance was not complete and onduction velocity at LBB was slower than at LBB although severe lesions were present at oth divisions Furthermore five cases of Groups 2 and 3 in which the conduction delay in both divisions was almost the same did not show LAD possibly because of cancellation between LBB and LBB_p While there is no consensus as yet regarding the concept of cancellation it represents an important hypothesis which is based on our control study and it should be pursued further

4 **The two versus three division theory in LBB** Our hypothesis regarding the LBB divisions is based on the consideration that there are two main portions consisting of the anterior and posterior radiation Demoulin and Kulbertus[4] and Massing and James[5] stated that the septal division is between the two main radiations However histologically the septal division appears to be a part of the posterior radiation with cellular communications between it and the posterior radiation Based on this consideration

Table IV Relationship between QRS axes and mode of conduction in LBB

Radiation		LBB_a			
	Mode of conduction	Normal	Slow	Slower	Block
LBB	Normal	NAD	PAD	RAD	RAD
	Slow	LAD	C	RAD	RAD
	Slower	LAD	LAD	C	RAD
	Block	LAD	LAD	LAD	LBBB

Normal normal conduction Slow slow conduction velocity Slower slower conduction velocity Block complete conduction disturbance C cancellation NAD nonaxis deviation RAD right axis deviation

LAD and RAD partly include QRS axes with tendency of LAD and PAD respectively

investigated portions more peripherally located than the blocks of Lev and colleagues method, our materials were comprised of relatively uniform hypertension cases, and we included control materials Therefore we consider our results to be reliable for evaluating the pathology of the conduction system in hypertensive hearts

Summary

We performed an electrocardiographic pathologic correlative study using the step sectioning method in 35 autopsy specimens from patients with hypertension

Eleven out of 12 cases (91 7%) in Group 1 had severe lesions at LBB or the His bundle and we propose that LAD in excess of −30 degrees is a good criterion in hypertension for LAH

There were six cases in all with severe lesions at both radiations of the LBB In one case of Group 1 LAD is suggested to be due to slower conduction at the LBB than at the LBB_p and findings in five cases of Groups 2 and 3 led us to speculate that there was no LAD because of cancellation between the LBB and the LBB_p

Histopathology revealed fibrosis degeneration, bleeding and calcification which pathogenetically may derive from mechanical strain effected by hypertension and metabolic changes in cases with chronic renal failure

REFERENCES

1 Rosenbaum M B., Elizari, M V and Lazzari, J O The hemiblocks, Oldsmar Fla., 1970 Tampa Tracings
2. Grant R P Left axis deviation An electrocardiographic pathologic correlative study Circulation 14 233, 1956
3 Pryor R., and Blount, S G The clinical significance of true left axis deviation AM. HEART J 72 391, 1967
4 Lev M., Rowlatt V F., and Runoldi, H J A Pathologic methods for study of congenitally malformed hearts AM HEART J 74 17 1961
5 Lev M., Widran J and Erickson, F E. A method for the histopathologic study of atrioventricular node, bundle and branches Arch Pathol. 52 73 1951
6 Sokolow M., and Lyon, T P The ventricular complex in left ventricular precordial and limb leads, AM HEART J 37 161 1949
7 Okada R Conduction system morphology Heart 5 [illegible] 1973
8 Demoulin J C and Kulbertus, H E. Histopathologic examination of concept of left hemiblock. Br Heart J 34 807 1972
9 Entman M L., Estes, E H., Hackel, D M and Durham N C The pathologic basis of the electrocardiographic pattern of parietal block, AM HEART J 74 202, 1967
10 Kulbertus H., Collignon, P., and Humblet, L. Vectorcardiographic study on the QRS loop in patients with left anterior focal block, AM HEART J 79 293, 1970
11 Gopal, D., Left axis deviation. A spectrum of intraventricular conduction block, Circulation 53 917 1976
12. Durrer D., Roos J P., and van Dam, R. T The genesis of the electrocardiogram of patients with ostium primum defects (ventral atrial septal defects) AM HEART J 71 642, 1966
13 Watt T B., Murao S., and Pruitt, R. D Left axis deviation induced experimentally in a primate heart, AM HEART J 70 381 1965
14 James T N., and Sherf L. Fine structure of the His bundle Circulation 9 44 1971
15 Massing G K., and James, T N Anatomical configuration of the His bundle and bundle branches in the human heart Circulation 53 609 1976.
16 Sugiura M., Okada, R Hiraoka, K., and Ohkawa S Histological studies in the conduction system in 11 cases of right bundle branch block associated with left axis deviation Jap Heart J 10 121 1969
17 Fukuda K Nakata Y., Sakurai, H Takagi, T Okada R., and Kitamura, K. Right bundle branch block and left axis deviation due to the calcification at the central fibrous body Heart 9 525 1977
18 Lev M Anatomic basis for atrioventricular block. Am J Med 37 742, 1964

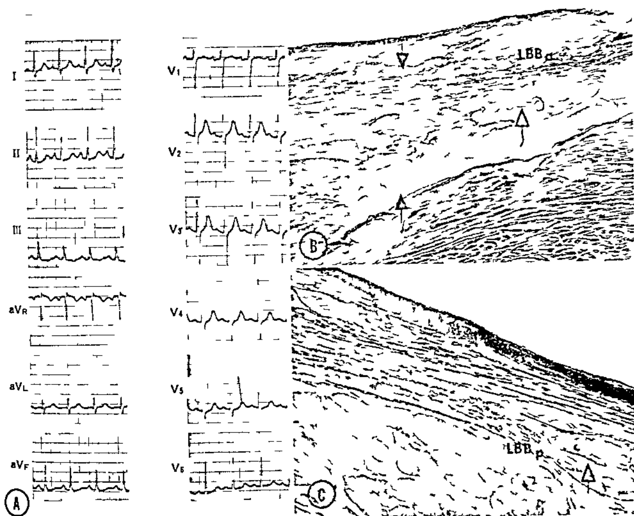


Fig 6 Case 4 *A* Electrocardiogram *B* Fatty degeneration and fibrosis *(solid arrows)* at LBB (Elastica Van Gieson stain original magnification ×40) *C* Marked fibrosis at LBB (Elastica Van Gieson stain original magnification ×100) *Open arrows* indicate conduction cells

we evaluated our data according to the two division theory

5 Conduction system morphology Regarding the cause of conduction disturbances Lev pro posed sclerosis of the left side of the cardiac skeleton and Sugiura and co workers suggested mechanical stain because they found that muco polysaccharides were increased in the fibrotic area In hypertension mechanical strain strongly affects the interventricular septum leading to hypertrophy of the septal wall which may lead to conduction disturbances due to compression of the conduction system

All materials in the present series were from patients with hypertension and seven of 12 (58%) of Group I specimens revealed fibrotic changes in the conduction system indicative of accumulated mechanical strain Degenerative changes were present in 60% of RH cases suggesting that metabolic changes due to chronic renal failure produced edema and fatty infiltration in the conduction system The massive bleeding into LBB which produced LAD in two of our present cases appears to have been due to rupture of weakened small vessels induced by mechanical strain in the septal wall The presence of a focal increase in catecholamines or other vasoactive substances is probable in these cases

6 Step sectioning method While we used the step (semi serial) sectioning method rather than the more precise serial sectioning method patho logical changes occur in relatively narrowly cir cumscribed areas of the conduction system and our sections included these Moreover we also

electrodes was introduced through the sheath and under fluoroscopic control was advanced into the right ventricle After satisfactory positioning the outer sheath was either left in place in the femoral vein or was withdrawn and secured All patients remained at bed rest while the pacing electrode was in place

Fibrinogen scan One hundred microcuries of [1] I labelled fibinogen was injected intravenously and a scan was performed in both lower extremities prior to the electrode insertion[9], the scan was then repeated daily The test was considered positive when the radioisotope counts on two consecutive days were more than 20% of the baseline precordial measurements [15] In addition a disparity in counts of more than 20% between two areas on the legs was considered positive The test was interpreted as negative when the counts were unchanged Counts that were between 10% and 20% of control and counts that were elevated for less than 24 hours were considered equivocal

Assay of fibrin degradation products Blood for the preparation of serum was collected into thrombin and epsilon amino caproic acid The staphylococcal clumping test method was used [1] employing bacterial preparations sensitive to 0 75 μg/ml of fibrinogen A concentration of less than 8 μg/ml was considered normal [1]

Impedance plethysmography All studies were performed by the same trained technician using the cuff occlusive technique and a cuff occlusion time of sufficient duration to obtain optimal filling [1] The maximum rise on the plethysmographic recording during cuff inflation and the fall in three seconds following cuff deflation were determined From these findings a numerical figure representing the venous function index was derived On the basis of the venous function index score the results were interpreted as positive negative or equivocal

Venography Venography on the affected leg was performed in four patients with equivocal findings in the noninvasive tests In the remaining patients in this category venography could not be performed because of the unwillingness of the patient or his physician The studies were evaluated by two independent radiologists

Results

The patient population consisted of 12 men and eight women The average age was 71 years (range 33 to 86 years) In 18 patients the right femoral vein was used in two patients the left femoral vein was used

Incidence Of the 20 patients evaluated, five patients (25%) fulfilled the criteria for deep vein thrombosis (Table I) One had positive findings in all of the noninvasive tests There were 1[illegible] patients with equivocal abnormalities in the noninvasive tests Four of these underwent venography and all four had positive venograms. Of these one had thrombosis of the femoral vein one had thrombosis in several calf veins and one had thrombosis in both the thigh and calf veins the fourth patient had thrombosis of the entire deep venous system of the extremity This patient was the only one who had clinical evidence of deep vein thrombosis

Tests performed on the contralateral extremity were consistently negative except in one patient in whom the fibrinogen scan was positive and another in whom the impedance plethysmography was positive Neither of these patients had evidence of deep venous thrombosis in their catheterized leg

Clinical background The clinical background of the patients is shown in Table I Patients with deep vein thrombosis did not differ from those without thrombosis with regard to recent myocardial infarction type of heart disease or history of congestive heart failure

Technical aspects related to the pacing procedure The number of venepunctures used for the introduction of the electrode varied from one to 10 but in 15 cases fewer than three punctures were necessary A new electrode was used in the cases and the introducer sheath was pulled out in 16 cases The length of time that the pacing catheter remained in place varied from one to 1[illegible] days with an average period of 3 4 days

There was no relationship between the occurrence of deep vein thrombosis and the number of venepunctures the presence of the outer sheath in the femoral vein or the duration of electrode use None of the patients in whom an old electrode was used developed thrombosis

Clinical sequelae None of the patients showed evidence of local or systemic infection There were no clinical features suggestive of pulmonary embolism in any of the patients

Discussion

The transfemoral approach provides a reliable simple and rapid technique for temporary pacing

Transfemoral temporary pacing and deep vein thrombosis

Natesa G Pandian M D
Bernard D Kosowsky M D
Victor Gurewich M D
Boston Mass

Transfemoral placement of a pacing catheter is a widely employed approach for temporary pacing[1,3] Few complications of this technique have been reported among which deep vein thrombosis has been only rarely mentioned [6] The clinical diagnosis of deep vein thrombosis has been shown to be unreliable [8] The development of reliable noninvasive tests[9,1] has provided the opportunity to evaluate the incidence of deep vein thrombosis associated with transfemoral pacing The diagnosis of deep vein thrombosis was based on I fibrinogen scanning impedance plethysmography and measurement of fibrin degradation products in all patients In four patients venography was also performed

Materials and methods

Patients who would require a temporary pacemaker for a minimum of 24 hours were studied Patients who were critically ill who were on anticoagulant therapy or who had a history of previous venous disease thromboembolic disease or hemoglobinopathies were excluded from the study During the period May 1978 to March 1979 20 patients were studied after obtaining informed consent Prior to the insertion of the pacemaker electrode I fibrinogen was injected impedance plethysmography was performed on both extremities and blood was drawn for fibrin degradation products Following pacer insertion the fibrinogen scan and assay of fibrin degradation products were obtained daily and impedance plethysmography was performed on alternate days Two observers made daily recordings of the presence or absence of leg pain edema tenderness change in leg and thigh circumference and Homans sign A study was terminated three days following the removal of the electrode unless the tests were positive at that time in which case they were continued until the tests returned to normal Whenever possible venography was performed in patients with equivocal results in the noninvasive tests Clinical information regarding the patients was not provided to the investigators analyzing the diagnostic tests

Based on the findings of clinical observation fibrinogen scan assay of fibrin degradation products impedance plethysmography and venography the following criteria were used to establish the diagnosis of deep vein thrombosis—*Present* venogram was positive or three of the other parameters were positive *Absent* venogram was negative or three of the other parameters were negative *Equivocal* results in neither of the above two categories

Method of electrode insertion Pacing was performed via the transfemoral route with a No 5 bipolar catheter by a modified Seldinger technique An 18 gauge thin walled needle was used to puncture the femoral vein A guidewire with a flexible tip was inserted through the needle and the needle was then replaced by a short Teflon inner catheter An outer dilating sheath was passed over the inner catheter The guide wire and the inner Teflon catheter were removed leaving only the outer sheath in the femoral vein A woven Dacron catheter with bipolar platinum

From th Dep rtm nt of Medicin (Card logv Di is on and Vascular Laborat ry) St Eliz beth s Hospital Tufts Un ers ty School of Med cin Bosto Mass

Recei ed fo publi t n Sept 26 19 9
Ac epted fo Publ at o D c 19 19 9

Reprint req ts Bern d D Kosow ky M D Card l gy D vision St. Elizabeth Hosp tal 736 Cambrid e St Brighto Mass 0 135

0009-8 03/80/190847 + 05$00.50/0 © 1980 The C V Mosby Co

and restriction of venous flow might have contributed to the genesis of the thrombosis

The patients with thrombosis did not differ clinically from those without deep vein thrombosis There was no relationship between the occurrence of deep vein thrombosis and the number of venepunctures or the presence of the introducer sheath in the femoral vein Our data are insufficient to derive a definite conclusion regarding the effect of the state of the electrode on the occurrence of thrombosis However none of the eight patients in whom an old sterilized electrode was used demonstrated deep vein thrombosis The occurrence of thrombosis did not seem to be influenced by the duration of pacing although all those with documented deep vein thrombosis had the electrode in place for at least 48 hours

The clinical significance of deep vein thrombosis in these patients is unclear None of our patients developed clinical evidence of pulmonary embolism One patient however, suffered severe temporary disability resulting from thrombosis of the entire deep venous system of the extremity used for pacing Some studies have demonstrated a high incidence of asymptomatic pulmonary emboli in patients with positive fibrinogen leg scan Others have questioned whether asymptomatic clotting in the veins of the lower leg has any serious sequelae

In conclusion deep vein thrombosis is a common complication of transfemoral pacing Although clinical symptoms are infrequent and adverse long term sequelae have not been demonstrated the high incidence of venous thrombosis with transfemoral pacing should be considered before deciding upon the site of entry for a temporary pacemaker Careful prospective analysis of the complications of the use of other entry sites will be necessary in order to make a rational choice Further studies are also necessary to determine if deep vein thrombosis associated with transfemoral pacing can be prevented by anticoagulants or other means

Summary

The incidence of deep vein thrombosis following transfemoral temporary pacing was prospectively assessed in 20 consecutive patients using serial I fibrinogen scanning impedance plethysmography and measurements of fibrin degradation products Four patients underwent venography Of the twenty patients five (25%) had definite evidence of deep vein thrombosis [illegible] demonstrated equivocal abnormalities and [illegible] had no evidence of thrombosis Thrombosis was found only in the legs used for pacing Of the five with deep vein thrombosis one had positive findings in all the noninvasive tests Venography confirmed the diagnosis in the other four one had thrombosis of the femoral vein one had thrombosis of several calf veins and one had thrombosis of both the thigh and calf veins the fourth patient had thrombosis of the entire deep venous system of the leg This latter patient was the only one who had clinical evidence of venous thrombosis The patients with deep vein thrombosis did not differ in clinical characteristics from those without thrombosis There was no relationship between the occurrence of deep vein thrombosis and the number of venepunctures the state of the electrode the presence of the introducer sheath in the femoral vein or the duration of pacing

In conclusion deep vein thrombosis is a common complication of transfemoral temporary pacing and the high incidence of its occurrence should be considered before deciding upon the site of entry for a temporary pacemaker

We are indebted to the staff of the Radiology and Nuclear Medicine Divisions St Elizabeth s Hospital and to the nursing personnel of our coronary care unit for their cooperation We are also grateful to Mary Ellen G Foti and Richard Tucker for their technical assistance

REFERENCES

1 Cheng T O Percutaneous transfemoral venous cardiac pacing a simple and practical method Chest 60 [illegible] 1971
2 Weinstein J Gnoj J Mazzara J T Ayers S M [illegible] Grace W J Temporary transvenous pacing via the percutaneous femoral vein approach Am Heart J 85 695 1973
3 Meister S G Banka V S and Helfant R H Transfemoral pacing with balloon tipped catheters JAMA 225 712 1973
4 Cohen S I Smith L K and Aroesty J M Transfemoral cardiac pacing and phlebitis Circulation 49 [illegible] 1019 1974
5 Furman S and Escher D J W Principles and Techniques of Cardiac Pacing New York 1970 Harper & Row pp 91 93
6 Meister S G Banka V S Chadda K D and [illegible] R H A balloon tipped catheter for obtaining [illegible] electrograms without fluoroscopy Circulation 49 [illegible] 1974
7 Kakkar V V The I labelled fibrinogen test and phlebography in the diagnosis of deep vein thrombosis Milbank Mem Fund 50 206 1972
8 Kakkar V V and Corrigan T P Detection of deep vein thrombosis survey and current status Progr Cardiovasc Dis 17 207 1974
9 Kakkar V V Nicolaides A N Renney J T C [illegible]

Table I Clinical data and results

Case no	Sex	Age	Clinical background	No of Punct	Electrode (new/old)	Sheath (in/out)	Duration electrode (days)	Clinical DVT	FS	IPG	FDP	Venogram	Conclusion
1	M	4	CAD AMI VT	1	New	In	5	Neg	Pos	Pos	Pos		Pos
2	M	52	CAD Old MI VT	4	New	Out	4	Neg	Pos	Neg	Pos		Eqv
3	M	33	VHD HB	1	New	Out	10	Neg	Neg	Neg	Neg		Neg
4	F	5	CAD Old MI	7	New	Out	2	Neg	Eqv	Eqv	Eqv		Eqv
5	M	5[illegible]	HB	1	New	Out	1	Neg	Neg	Neg	Eqv		Neg
6	M	[illegible]4	CHF VT	1	New	Out	8	Neg	Neg	Eqv	Pos		Eqv
	F	79	HB	1	Old	Out	2	Neg	Neg	Neg	Neg		Neg
8	M	[illegible]	CAD Old MI VT	2	New	Out	3	Neg	Neg	Neg	Eqv		Neg
9	M	81	CAD Old MI	1	New	Out	2	Neg	Neg	Pos	Eqv	Pos	Pos
10	M	82	HB	1	New	Out	3	Neg	Eqv	Eqv	Pos	Pos	Pos
11	F	8[illegible]	A FIB	2	Old	Out	4	Neg	Neg	Eqv	Pos		Eqv
12	M	8	CHF HB	2	Old	Out	1	Neg	Neg	Neg	Pos		Neg
13	F	8	HB	1	New	Out	3	Neg	Neg	Neg	Pos		Neg
14	F	69	HB	1	Old	In	1	Neg	Pos	Eqv	Eqv		Eqv
15	F	[illegible]	HB	5	Old	In	1	Neg	Neg	Pos	Pos		Eqv
16	M	86	Ca A FIB	1	Old	In	[illegible]	Neg	Neg	Neg	Pos		Neg
17	F	6	HB	2	Old	Out	1	Neg	Neg	Neg	Neg		Neg
18	M	71	A FIB	6	New	Out	4	Pos	Neg	Pos	Pos		Pos
19	M	4	HB VT	10	Old	Out	1	Neg	Neg	Eqv	Eqv		Neg
20	F	[illegible]	CHF HB VT	2	New	Out	6	Neg	Pos	Neg	Pos	Pos	Pos

Pos = positive Neg = negative Eqv = equivocal Punct = no. of punctures FS = fibrinogen scan IPG = impedance plethysmography FDP = fibrin degradation products DVT = deep vein thrombosis CAD = coronary artery disease CHF = congestive heart failure MI = myocardial infarction AMI = acute myocardial infarction VT = ventricular tachycardia HB = heart block A FIB = atrial fibrillation VHD = valvular heart disease Ca = carcinomatous disease

Abnormal in contralateral leg

It is widely employed since it is thought to be relatively free of complications. Despite the frequent use of this approach, reports of deep vein thrombosis of the lower extremities are uncommon. In a retrospective series of 80 patients, Cohen and associates noted the occurrence of deep vein thrombosis in five patients. Of 267 patients with transfemoral pacing reported by Furman and co-workers, only one was found to have had clinical evidence of iliofemoral phlebitis. In several other large series of consecutively paced patients using the transfemoral route, no instance of deep vein thrombosis was noted.

Our study demonstrates a high incidence of venous thrombosis as a complication of transfemoral pacing. The diagnosis was made in five of 20 patients studied. Only one patient had positive findings in all of the noninvasive tests. There were 10 patients with equivocal abnormalities in the noninvasive tests, of whom only four underwent venography; all four had thrombosis of the deep venous system. It is possible that some of the six remaining patients with equivocal results in the noninvasive studies might have demonstrated deep vein thrombosis had venography been performed. Thus the incidence of thrombosis might indeed be higher than the 25% noted. The rarity of reports of thrombotic complications is probably due to the fact that thrombosis is usually not clinically apparent. In our study only one patient had symptoms and physical findings suggestive of deep vein thrombosis.

The occurrence of deep vein thrombosis can be attributed to several factors associated with routine transfemoral pacing. These include venepuncture, the presence of a foreign body, partial venous obstruction, and extended periods of bed rest. Infection can be a cause of thrombosis, but this did not appear to be a factor in these cases. Although our patients remained at bed rest, mobility of the extremity used for pacing was not selectively limited, yet deep vein thrombosis occurred only in the extremity used for pacing. It is noteworthy that all our patients who had venograms had clots distal to the site of entry of the electrode. Thus partial venous obstruction

The effects of vasoconstriction on experimental coronary artery stenosis

William P Santamore, Ph D *
Paul Walinsky, M D
Alfred A Bove M D Ph D F A C C
Robert H Cox Ph D
Rita A Carey Ph D
James F Spann M D F A C C
Philadelphia Pa

There is little doubt at present that coronary artery spasm is an important mechanism in the production of angina pectoris Several recent studies have also demonstrated the presence of coronary spasm in preexisting atherosclerotic lesions of the coronary arteries and have suggested [illegible] spasm may be responsible for myocardial [illegible] in some patients [1-11] Implicit in these [illegible] observations is the ability of large proximal coronary arteries to constrict and thereby [illegible] their luminal area From postmortem examination Masen and colleagues demonstrated that areas of stenosis often contain an arterial wall segment which is normal and apparently able to contract To properly study this type of lesion we have developed an in vitro arterial preparation which resembles hemodynamically the coronary lesion in man This model is achieved by obstructing flow through the artery with an intraluminal device which allows a stenosis to be created while still allowing arterial vasoconstriction to occur When the effects of active arterial vasoconstriction were examined in this model in the presence of an otherwide mild fixed stenosis a striking alteration in the hemodynamics of the stenosis was noted In effect the partial stenosis even when mild caused severe occlusion in the presence of arterial vasoconstriction This finding provides some insight into the effects of spasm on coronary flow in man

Methods

The effects of arterial vasoconstriction on stenotic hemodynamics were examined in an in vitro coronary artery preparation An in vitro preparation was used to eliminate distal coronary vasculature neural humoral and systemic effects Eight mongrel dogs (weighing 11.3 to [illegible] kilograms) were anesthetized with sodium pentobarbital (30 mg/kg) and their hearts were exposed through a left lateral thoracotomy The hearts were removed (while still beating) and were placed in a cold physiologic salt solution (5° C) The hearts were kept in the physiological salt solution while the proximal circumflex coronary arteries from the aortic root to the anterior ventricular marginal branch were carefully dissected free from the surrounding tissue All branch arteries along this section of the circumflex artery were ligated and cut distally The distal portion of the circumflex artery was cut [illegible] the anterior ventricular marginal branch and the proximal portion including part of the aortic root was also cut The above procedure required between 30 to 45 minutes to remove the first 3 to [illegible] cm of the proximal circumflex artery After removal four arteries were placed in a physiologic salt solution stored in a refrigerator overnight and studied the next day The remaining arteries were immediately attached to the perfusion appa

From Temple University Medical School Department of Medicine Division of Cardiology and Jefferson Medical College Department of Medicine Philadelphia

Received for publication [illegible]

Accepted for publication [illegible] 14 1980

Reprint requests William P Santamore Ph D Temple University Medical School Dept of Medicine Philadelphia Pa 19140

* Special Investigator of the Southeastern Pennsylvania Heart Association

0002-8703/80/1208[illegible] + 0[illegible] 0/0 © 1980 The C V Mosby Co

Friend J R [125]I labelled fibrinogen test adapted for routine screening for deep vein thrombosis Lancet 1 540 1970
10 Evans, D S and Cockett F B Diagnosis of deep vein thrombosis with an ultrasonic Doppler technique Br Med J 2 802 1969
11 Mullick S C Wheeler H B and Songster G F Diagnosis of deep vein thrombosis by measurement of electrical impedance Am J Surg 119 417 1970
12 Hawiger J Niewiarowski, S Gurewich V and Thomas, D P Measurement of fibrinogen and fibrin degradation products in serum by staphylococcal clumping test J Lab Clin Med. 75 93 1970
13 Seldinger S I Catheter replacement of the needle in percutaneous arteriography Acta Radiol 39 368 1953
14 Solomon N and Escher D J W A rapid method for insertion of the pacemaker catheter electrode AM HEART J 66 717 1963.
15 Kakkar V V., Howe C T Nicolaides A N Renney J T G and Clark M B Deep vein thrombosis of the leg Is there a high risk group? Am J Surg 120 52 1970
16 Thomas D P Niewiarowski, S Myers A R Bloch K J and Colman R W A comparative study of four methods for detecting fibrinogen degradation products in patients with various diseases, N Engl J Med 283 663 1970
17 Wheeler H B O Donnell J A Anderson F A and Benedict K Occlusive impedance phlebography A diagnostic procedure for venous thrombosis and pulmonary embolism Progr Cardiovasc Dis 27 199 1974
18 Hull R Taylor D W Hirsh J Sackett D L Powers, P Turpie A G G and Walker I Impedance plethysmography The relationship between venous filling and sensitivity and specificity for proximal vein thrombosis Circulation 58 898 1978
19 Wheeler H B Anderson F A Matesanz J M and Larsen J E Impedance plethysmography *in* Noninvasive Techniques in Vascular Disease Bernstein E F ed St Louis 1978 The C V Mosby Company pp 359 373
20 Foti M E G and Gurewich V Determination of fibrin degradation products and impedance plethysmography in the diagnosis of deep vein thrombosis Circulation 58(Suppl II) 116 1978
21 Lahnborg G Bergstrom K Friman L and Lagergren H Effect of low-dose heparin on incidence of postoperative pulmonary embolism detected by photoscanning Lancet 1 329 1974
22 Blaisdell, F W Low-dose heparin prophylaxis of venous thrombosis an editorial AM HEART J 97 685 1979

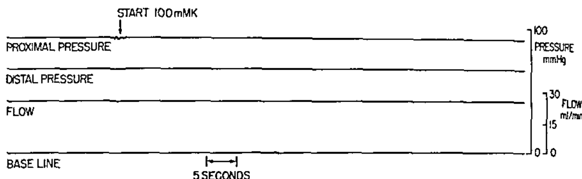


Fig 2 Typical stenotic hemodynamic response to coronary artery vasoconstriction with an external circumferential snare

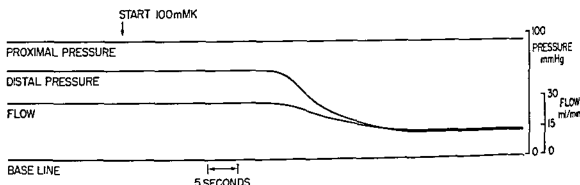


Fig 3 Typical stenotic hemodynamic response to coronary artery vasoconstriction with an intraluminal obstruction

arterial bath solution was drained and was refilled with the 1 5 mMK physiologic salt solution

Next in the presence of an external constrictor the hemodynamic response to arterial vasoconstriction was examined External constriction was achieved by a circumferential snare The snare consisted of a 1 0 silk suture passed around the artery through the polyethylene 160 tubing and attached to a machinist s micrometer This is a commonly used technique to achieve arterial stenosis[1] The artery was perfused with 1 5 mMK physiologic salt solution and the snare was tightened to create a pressure gradient across the stenosis The variables were recorded for 10 minutes to varify stability The perfusate was switched to the 100 mMK salt solution and the variables were recorded for 5 minutes The artery was reperfused with the 1 5 mMK physiologic salt solution the bath solution was drained and refilled with the 1 5 mMK physiologic salt solution The above procedure was repeated two times on each artery studied

Finally the response to arterial vasoconstriction in the presence of internal obstruction was examined Internal obstruction (*Fig 1b*) was achieved by a 3F Fogarty balloon catheter The artery was perfused with the 1 5 mMK physiologic salt solution and the balloon was inflated to create a pressure gradient across the artery Note that the maximum arterial diameter was determined by the perfusion pressure Therefore the balloon did not and could not have created a bulge in the artery while still allowing flow through the artery The Fogarty balloon catheter was inflated with an acrylic solution which solidified within 1/2 hour (*JB-4 Polysciences Inc*) The acrylic solution insured a fixed stable intraluminal obstruction The variables were recorded for 30 minutes to verify stability and to allow the acrylic solution to solidify The perfusate was switched to the 100 mMK salt solution and the variables were recorded for five minutes Provided there was still a perfusion flow the artery was reperfused with the 1 5 mMK salt solution the arterial bath was drained and refilled with the 1 5 mMK physiologic salt solution When the internal obstruction plus the 100 mMK salt solution

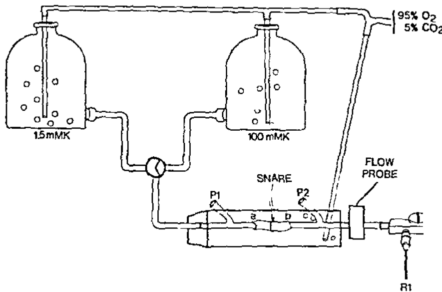


Fig 1a Diagram of in vitro constant pressure perfusion system External constrictor *P1* = proximal pressure *P2* = distal pressure *a* = proximal and *b* = distal points of attachment for artery *P1* – 20 gauge Longdwel needle

ratus and were studied There was no difference in response between the arteries studied after overnight storage in refrigerated physiologic salt solution and those used immediately

The perfusion apparatus (Fig 1*a*) consisted of two pressure reservoirs an arterial bath and fixed distal resistance One reservoir contained a 1.5 mMK physiologic salt solution (composition in millimoles per liter 122 0 NaCl 25 0 $NaHCO_3$ 1 2 NaH_2PO_4 1 2 $MgSO_4$ 1 5 KCl 2 5 $CaCl_2$ and 10 pyruvic acid pH = 7 42) while the other reservoir contained a 100 mMK solution (composition in millimoles per liter 24 NaCl 25 $NaHCO_3$ 1 2 NaH_2PO_4 1 2 $MgSO_4$ 100 KCl 2 5 $CaCl_2$ 10 pyruvic acid pH = 7 42) The arterial bath was filled with the 1.5 mMK physiologic salt solution All solutions were maintained at 37° C and were equilibrated with a gaseous mixture of 95% O_2 5% CO_2 The distal resistance was a 20 gauge Longwel needle Proximal and distal pressures were measured with pressure transducers (Statham) Perfusion flow was measure with an extracorporeal flow probe (Biotronex) This flow probe was calibrated by a timed collection in a graduated cylinder The data were recorded on a multichannel recorder (Electronics for Medicine model DR-8)

The artery was placed in the bath solution attached to point a and b (Fig 1*a*) and stretched to its in vivo length The reservoir pressure was applied to the arterial segment and the artery was allowed to stabilize for two hours The reservoir pressure and the arterial length were kept constant throughout the experiment

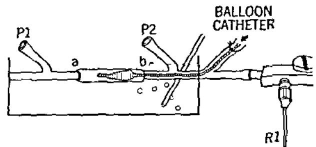


Fig 1b Diagram of in vitro constant pressure perfusion system Internal obstruction Abbreviations and symbols same as in *Fig 1a*

Prior to creating the stenosis the hemodynamic response to arterial vasoconstriction was examined The distal stopcock was opened and the perfusate was allowed to flow through the artery The variables were recorded while the artery was perfused with the 1 5 mMK physiologic salt solution After five minutes the perfusate was then switched to the 100 mMK salt solution and the variables were recorded Changing from a 1 5 mMK solution to a 100 mMK solution causes consistent coronary artery vasoconstriction After five minutes the artery was reperfused with the 1 5 mMK physiologic salt solution and the

Table I Hemodynamic effects of coronary artery vasoconstriction

	Proximal pressure (mm Hg)	*Distal pressure (mm Hg)*	*Flow (ml/min)*	*Stenotic resistance (mm Hg/ml min)*	*Distal resistance (mm Hg/ml min)*	*Proximal diameter (cm)*	*Di l diam (cm)*
No constriction							
1 5 mMK	94 7	91 1	31 1	–	2 94	3 1	–
	± 1 2	± 1 3	± 1 0		± 0 08	± 0 3	
100 mMK	94 5	90 5	30 1	–	3 0	3 0	–
	± 1 6	± 1.8	± 1 4		± 0 13	± 0 3	
External constriction							
1 5 mMK	93 0	68 4	25.9	1 07	2 66	3 1	*9
	± 1 8	± 4 9	± 2 0	± 0 25	± 0 07	± 0 1	±01
100 mMK	93 5	68 0	25 5	1 13	2 68	3 1	*9
	± 2 0	± 5 3	± 2 0	± 0 28	± 0 09	± 0 1	±01
Internal obstruction							
1 5 mMK	94 9	69.3	2' 1	1 12	2 5?	3.2	29
	± 0 9	± 4 9	± 1 7	± 0 29	± 0 07	± 0 1	±01
100 mMK	94 9	18 2*	11 8	10 6?	1 ?6	3 1	?0
	± 1 0	± 5 6	± 2 0	± 2 86	± 0 2	± 0 1	0?

All data values are mean ± standard error of mean
* P < 0 01 compared to 1 5 mMK response by Student s t test

vasodilation on pressure and flow in a stenosis that was created with the intraluminal balloon After obtaining the response described in Fig 3 the perfusate was switched back to a 1 5 mMK physiologic salt solution This reperfusion resulted in a return of flow and an increase in distal pressure thus allowing the initial stenotic hemodynamics to be restored It should be pointed out that if the flow reduction caused by arterial vasoconstriction was severe (flow less than 1 ml/minute) reperfusion was ineffective in reestablishing the initial conditions because the 1 5 mMK solution could not reach the stenotic site In these experiments nitroglycerin (0 4 mg) was added to the arterial bath solution This reestablished the initial stenotic hemodynamics

Table I summarizes the results from the eight coronary arteries studied Table I is based upon eight observations with no constriction 16 observation with external constriction and 24 observations with an internal obstruction The diameter data are from two experiments Prior to the creation of an arterial steno is vasoconstriction had no significant effect on the measured and calculated variables Similarly with arterial stenosis produced by an external circumferential snare arterial vasoconstriction had no significant effect on the measured and calculated variables In striking contrast with stenosis produced by an intraluminal balloon catheter arterial vasocon striction caused significant hemodynamic changes Distal pressure flow and di tal diameter decreased and the stenotic resistance increased markedly Thus internal obstruction potentiated the effects of arterial vasoconstriction causing significant hemodynamic chan

Discussion

This is the first experimental model where a reduction in flow through the coronary artery has been achieved by proximal coronary artery vasoconstriction Other animal experiments h e shown a coronary flow reduction caused by vasoconstriction along the entire coronary vascula ture However this is the *only* animal model where proximal coronary artery con triction alone (vasoconstriction along the first 3 cm of the coronary artery) has been able to reduce flow through the vessel In light of the current cli ical interest in coronary artery spasm where the major pathophysiological mechanism appears to be an abnormal contraction in the proximal coronary artery this animal model is an impor tant first step in understanding some of the hemodynamics of coronary artery spasm

This study demonstrates the striking hemodynamic effect of arterial vasoconstriction when a partial luminal obstruction is pre ent Neither the arterial vasoconstriction alone in the normal vessel nor the stenosis alone cau ed a significa t

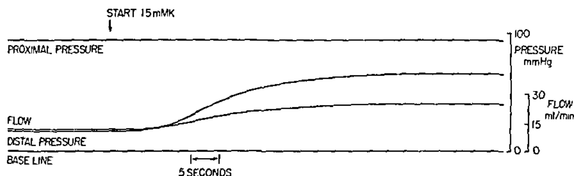


Fig 4 Typical stenotic hemodynamic response to coronary artery vasodilation with an intraluminal obstruction

caused the perfusion flow to cease nitroglycerin (0 4 mg) was added to the bath This always caused a relaxation of the artery and reestablished the normal perfusion flow The above procedure except for inflating the balloon was repeated three times on each artery studied

In the last two experiments the diameters of the circumflex artery proximal and distal to the stenotic site were measured with a calibrated eyepiece (magnification 7×) The diameters were measured just before and during the perfusion with the 100 mMK salt solution

The stenotic resistance was calculated as the pressure gradient across the stenosis divided by the flow throught the stenosis [1] the pressure gradient being the proximal pressure minus the distal pressure The distal resistance was calculated as the distal pressure divided by the flow The stenotic and distal resistances were only calculated when the flow was greater than 1 0 ml/minute In each data group the mean and the standard error of the mean were determined for the proximal pressure distal pressure flow stenotic resistance and distal resistance Statistical significance was determined by comparing the 15 mMK response to the 100 mMK response by the Student s t test [1]

Results

Fig 2 shows the effects of coronary artery vasoconstriction on pressure and flow in the artery An initial stenosis was created with an external circumferential snare With a 1 5 mMK physiologic salt solution perfusing the artery the initial *stenosis was established and allowed to* stabilize for ten minutes The perfusate was switched to a 100 mMK salt solution indicated *by the arrow* in Fig 2 The 100 mMK solution was

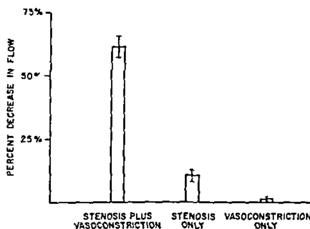


Fig 5 Diagram showing synergistic effects of stenosis and vasoconstriction on reducing flow

used to induce arterial vasoconstriction As can be seen in Fig 2 maximum arterial vasoconstriction caused no observable effects on the flow through and the pressure across the stenosis produced by an external circumferential snare

Fig 3 shows the effects of coronary artery vasoconstriction on pressure and flow in a stenosis that was created with an intraluminal Fogarty balloon catheter With a 1 5 mMK physiologic salt solution perfusing the artery the initial stenosis was established and was allowed to stabilize for 30 minutes The perfusate was then switched to a 100 mMK salt solution As can be seen in Fig 3 arterial vasoconstriction severely reduced the flow through and increased the pressure across the stenosis Thus *stenoses created by* internal obstruction were extremely sensitive to arterial vasoconstriction

Fig 4 shows the effects of coronary artery

of coronary arterial spasm Clinical angiographic and myocardial metabolic experience in 29 cases Am J Cardiol 38 945 1976
3 Schroeder J S Bolen J L Quint R A Clark D A Hayden W G Higgins C B and Wexler L Provocation of coronary spasm with ergonovine maleate New test with results in 57 patients undergoing coronary arteriography Am J Cardiol 40 487 1977
4 Curry R C Pepine C J Sabom M B Feldman R L Christie L G and Conti C R Effects of ergonovine in patients with and without coronary artery disease Circulation 56 803 1977
5 Mudge G H Jr Grossman W Mills R M Jr Lesch M and Braunwald E Reflex increase in coronary vascular resistance in patients with ischemic heart disease N Engl J Med 295 1333 1976
6 Yasue H Nagao M Omote S Takizawa A Miwa K and Tanaka S Coronary arterial spasm and Prinzmetal s variant form of angina induced by hyperventilation and Tris buffer infusion Circulation 58 56 1978
7 Curry R C Jr Pepine C J Sabom M B Feldman R L Christie L G Varnell J H and Conti C R Hemodynamic and myocardial metabolic effects of ergonovine in patients with chest pain Circulation 58 648 1978
8 Maseri A L Abbate A Baroldi G Chierchia S Marzilli M Ballestra A M Severi S Parodi O Biagini A Distante A and Pesola A Coronary vasospasm as a possible cause of myocardial infarction A conclusion derived from the study of preinfarction angina N Engl J Med 299 1271 1978
9 Curry R C Jr Pepine C J Sabom M B and Conti C R Similarities of ergonovine induced and spontaneous attacks of variant angina Circulation 59 307 1979
10 Madias J E The syndrome of variant angina culminating in acute myocardial infarction Circulation 59 297 1979
11 Mudge G H Jr Goldberg S Gunther S Mann T and Grossman W Comparison of metabolic and vasoconstrictor stimuli on coronary vascular resistance in man Circulation 59 544 1979
12 Waters D D Chaitman B R Dupras G Theroux P and Mizgala H F Coronary artery spasm during exercise in patients with variant angina Circulation 59 580 1979
13 Oravetz R Lee G Baker L Titus P Joye J A Kaku R Bogren H and Mason D T Pronounced dilation of stenotic coronary artery lesions following sublingual nitroglycerin by quantitative arteriography Circulation 58 II 25 1978
14 Borda L Shuchleib R and Henry P D Effects of potassium on isolated canine coronary arteries modulation of adrenergic responsiveness and release of norepinephrine Circ Res 41 778 1977
15 Nakayama K Fleckenstein A Byon Y K and Fleckenstein Gron G Fundamental physiology of coronary smooth musculature from extramural stem arteries of pigs and rabbits (Electric excitability tension development influence of Ca Mg H and K ions) Europ J Cardiol 8 319 1978
16 Gould K L Lipscomb K and Hamilton G W Physiologic basis for assessing critical coronary stenosis Am J Cardiol 33 87 1974
17 Burton A C Physiology and biophysics of the circulation Chicago 1972 Year Book Medical Publishers Inc p 89
18 Guilford J P Fundamental statistics in psychology and education New York 1965 McGraw Hill Book Company Inc pp 181 185
19 Mates R E Gupta R L Bell A C and Klocke F J Fluid dynamics of coronary artery stenosis Circ Res 42 152 1978
20 Alexander R S Critical closure reexamined Circ Res 40 531 1977

flow change but when present together they act synergistically to produce a marked reduction in the arterial lumen, a large pressure gradient, and a significant reduction of flow (see Fig. 5).

Conversely, with partial stenosis created by a circumferential snare, subsequent arterial vasoconstriction had little effect on stenotic hemodynamics. The initial stenotic resistance, flow, and distal pressure (see Table I) were almost identical for stenoses created by either an external snare or by an intraluminal obstruction. Yet with external snare, arterial vasoconstriction was ineffective. Conceivably, the external snare shortened the circumferential vessel fibers to a maximal degree so that no further shortening was possible by vasoconstriction. This observation may be relevant to the clinical situation where although two patients may have a similar degree of stenosis, only one patient will exhibit coronary artery spasm.

With the internal obstruction, arterial vasoconstriction could have increased the hemodynamic severity of the stenosis by a slight reduction in the vessel radius at the stenotic site. In an otherwise normal vessel a 5% reduction in radius would cause approximately a 10% reduction in vessel area. With an initial stenosis of 85 to 90%, a 5% reduction in vessel radius can occlude the artery. Also, the Bernoulli Principle might increase the effectiveness of the vasoconstriction. According to Bernoulli's equation, the pressure by the stenosis is reduced.[1] This stenotic pressure decrease would allow the vessel to constrict even further; the lower the intraluminal pressure, the greater the resulting vessel radius decrease for the same vasoconstriction stimulus.

There is increasing evidence in man that some episodes of angina pectoris may be caused by arterial spasm superimposed on the atherosclerotic stenosis of a major coronary artery. In these patients, coronary artery spasm can be induced by intravenous ergonovine maleate or by hyperventilation combined with tris buffer infusion and can be relieved by nitroglycerin. Coronary angiograms have shown a decrease in vessel diameter or actual closure of the vessel during angina attacks in some patients. Nitroglycerin caused these vessels to dilate. These clinical studies suggest that angina pectoris and myocardial infarction are in part associated with dynamic spasm becoming additive to fixed lesions of the coronary arteries in some patients.

Indeed, Maseri and co-workers have used postmortem studies to demonstrate that areas of atherosclerotic stenosis often contain a wall segment which is normal and apparently able to contract. In this study, stenosis created by an intraluminal balloon catheter exhibited characteristics similar to the clinical lesion; the arterial wall is able to contract, arterial vasoconstriction increased stenotic severity, and dilation decreased stenotic severity. We believe that this type of response is a reasonable model for at least some of the stenotic lesions found in coronary artery disease.

In our experiments, if the flow reduction after arterial vasoconstriction was severe, then reperfusion with the 1.5 mMK physiologic salt solution was ineffective in relieving the spasm, possibly because the 1.5 mMK solution never reached the stenotic site. If arterial spasm in man resulted in temporary total occlusion with absence of flow, the vasoconstriction may become irreversible because removal of the vasoconstricting stimulus, if it was blood borne, would be impossible.

Summary

In summary, we have examined the response to arterial vasoconstriction in an in vitro coronary artery preparation. Without a preexisting stenosis, arterial vasoconstriction had minimal hemodynamic effects. Similarly, with a stenosis created by a circumferential snare, arterial vasoconstriction had minimal hemodynamic effects. In striking contrast, with a stenosis created by intraluminal obstruction, arterial vasoconstriction dramatically increased the hemodynamic severity of the stenosis. The use of an intraluminal obstruction provides a useful animal model for examining hemodynamics in coronary artery disease and has provided some insight into the effects of vasoconstriction on coronary artery hemodynamics. Obviously, this is an experimental study, and care must be taken in extrapolating these results to diseased human coronary arteries.

The authors gratefully acknowledge the technical assistance of Thomas Vinciguerra, David Santamore, and John Michele.

REFERENCES

1. Maseri A, Mimmo R, Chierchia S, Marchesi C, Pesola A, and L'Abbate A: Coronary artery spasm as a cause of acute myocardial ischemia in man. Chest 68:625, 1975.
2. Wiener L, Kasparian H, Duca P R, Walinsky P, Gottlieb R S, Hanckel F, and Brest A N: Spectrum

of coronary arterial spasm Clinical, angiographic and myocardial metabolic experience in 2J cases Am J Cardiol 38 945 1976

3 Schroeder J S Bolen J L Quint R A Clark D A Hayden W G Higgins C B and Wexler L Provocation of coronary spasm with erognovine maleate New test with results in 57 patients undergoing coronary arteriography Am J Cardiol 40 487 1977

4 Curry R C Pepine C J Sabom M B Feldman R L Christie L G and Conti C R Effects of ergonovine in patients with and without coronary artery disease Circulation 56 803 1977

5 Mudge G H Jr Grossman W Mills R M Jr Lesch M and Braunwald E Reflex increase in coronary vascular resistance in patients with ischemic heart disease N Engl J Med 295 1333 1976

6 Yasue H Nagao M Omote S Takizawa A Miwa K., and Tanaka, S Coronary arterial spasm and Prinzmetal s variant form of angina induced by hyperventilation and Tris buffer infusion Circulation 58 56 1978

7 Curry R C Jr Pepine C J Sabom M B Feldman R L Christie L G Varnell J H and Conti, C R Hemodynamic and myocardial metabolic effects of ergonovine in patients with chest pain Circulation 58 648 1978

8 Maseri A L Abbate A Baroldi G., Chierchia S Marzilli M Ballestra A M Severi S Parodi O Biagini A Distante A and Pesola A Coronary vasospasm as a possible cause of myocardial infarction A conclusion derived from the study of preinfarction angina, N Engl J Med 299 1271 1978

9 Curry R C Jr Pepine C J Sabom M B and Conti C R Similarities of ergonovine induced and spontaneous attacks of variant angina Circulation 59 307 1979

10 Madias J F The syndrome of variant angina culminating in acute myocardial infarction Circulation 59 297 1979

11 Mudge G H Jr Goldberg S Gunther S M... T and Grossman W Comparison of metabolic and ... constrictor stimuli on coronary vascular resistance ... man Circulation 59 544 1979

12 Waters D D Chaitman B R Dupras G Theroux P and Mizgala H F Coronary artery spasm during exercise in patients with variant angina Circulation 59 580 19 9

13 Oravetz R Lee G Baker L Titus, P Joye J A Kaku R Bogren H and Mason D T Pronounced dilation of stenotic coronary artery lesions following sublingual nitroglycerin by quantitative arteriography Circulation 58 II 25 1978

14 Borda L Shuchleib R and Henry P D Effects of potassium on isolated canine coronary arteries mod... tion of adrenergic responsiveness and release of norepinephrine Circ Res 41 778 19..

15 Nakayama K Fleckenstein A Byon Y K, and Fleckenstein Grun G Fundamental physiology of coronary smooth musculature from extramural stem arteries of pigs and rabbits (Electric excitability tension development influence of Ca Mg H and K ions) Eur J Cardiol 8 319 1978

16 Gould K L Lipscomb K and Hamilton, G W Physiologic basis for assessing critical coronary stenosis Am J Cardiol 33 87 1974

17 Burton A C Physiology and biophysics of the circulation Chicago 1972 Year Book Medical Publishers, Inc p 89

18 Guilford J P Fundamental statistics in psychology and education New York, 1965 McGraw Hill Book Company Inc., pp 181 18..

19 Mates R E Gupta R L Bell A C and Klocke F J Fluid dynamics of coronary artery stenosis, Circ Res 42 152 1978

20 Alexander R.S Critical closure reexamined Circ Res 40 531 1977

Case reports

Right ventricular endomyocardial fibrosis simulating Ebstein s anomaly

Massoud Alipour M D F R C P(C) F A C C*
Cyavoush Tarbiat M D *
Iraj Nazarian M D **
Tehran Iran

Clinical features and the usual laboratory data as well as cardiac catheterization findings may fail to differentiate right ventricular endomyocardial fibrosis (RVEF) from Ebstein s anomaly

Since RVEF is correctable by surgery at least potentially differentiation of these cases from Ebstein s anomaly is important and the latter also may require surgical intervention

Accurate bedside diagnosis of RVEF is some times possible however tricuspid regurgitation occasionally associated with a tricuspid diastolic flow may be confused with rheumatic heart disease[1]

This report is concerned with a case of RVEF which was operated on with a preoperative diag nosis of Ebstein s anomaly

Case History

A T a 20 year-old man was admitted in January 1975 with a six year history of exertional dyspnea, progressive swelling of the face and abdomen slight bilateral ankle edema with small varicose veins and moderate mucocutaneous cyanosis

There was neither history of rheumatic fever during child hood nor cyanosis at birth Conjunctivae and oral mucosa were congested jugular veins were engorged and the top of the venous column was seen at mandibular angle at 45 degree trunk elevation without prominent pulsation Pulses were of low volume and blood pressure was 100/70 mm Hg The patient was afebrile Kussmaul s sign and paradoxical pulse were absent

From the Divisions of Adult Cardiology Cardiovascular Surgery and Pathology Heart Hospital Tehran Iran

Received for publication May 31 1979

Accepted for publication June 9 1979

Reprint requests M S Alipour M D Division of Adult Cardiology Heart Hospital Mosadegh Road Tehran Iran

*Division of Adult Cardiology Heart Hospital

*Division of Cardiovascular Surgery Heart Hospital

Division of Pathology Heart Hospital

The precordium was quiet The first heart sound was widely split with very prominent second component A soft pansystolic murmur was initially heard at the patient s first physical examination at the right lower sternal border which was accentuated by inspiration At his second admission in 19 when his congestive heart failure was severe this murmur could hardly be heard without any change in inspiration Right ventricular gallop was present at both admissions A and P were physiologically split and were normal in intensity

A few bilateral basal crepitant rales were present initially which cleared soon following digoxin and diuretic therapy A moderate amount of ascites was present The liver was enlarged 4 cm below the right costal margin

Hepatic systolic pulsation which was present at his first admission in 19 5 was not felt at the second admission and it was thought that the liver was slightly smaller

Slight pitting edema and many small varicose veins were observed mostly around the ankles Moderate clubbing was present

Electrocardiogram and chest roentgenogram The electrocardiogram showed atrial fibrillation and a pattern of incomplete right bundle branch block (RBBB) (Fig 1) A chest x ray revealed an enlarged balloon shaped heart with a very prominent right atrium and a narrow vascular pedicle The enormous cardiac shadow contrasted with oligemia of the lung fields (Fig 2)

Echocardiogram The first echocardiogram was interpreted as simultaneous tricuspid and mitral valve echograms Two leaflets of the tricuspid valve could be seen during the entire cardiac cycle simulating a pattern of tricuspid stenosis The time difference between the mitral and tricuspid closure was too long almost half a cardiac cycle Scanning from the aorta to the mitral area revealed normal aorto mitral continuity and the anterior wall of the aorta was in continuation with what we thought was the tricuspid valve (Figs 3 and 4)

Catheterization data and intracardiac electrocardiogram Catheter manipulation did not induce significant arrhythmias Atrial septal defect or patent foramen ovale was not found Entering the right ventricle and pulmonary artery was not easy Leftward displacement of the tricuspid valve was noted during angiography and pressure curve recording (Fig 5) Arterial oxygen saturation was low (82%) Mean right atrial pressure was high (24 mm Hg) Right ventricular

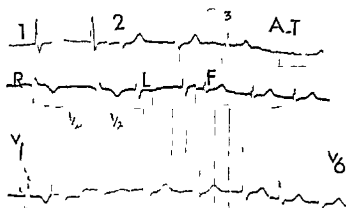


Fig 1 Atrial fibrillation and a pattern of incomplete right bundle branch block are shown in this ECG tracing



Fig 2 A chest x ray shows the enlarged balloon shaped heart with a narrow pedicle and a prominent right atrium

systolic pressure was 40 mm Hg with a high end diastolic pressure of 24 mm Hg The right ventricular pressure curve had a dip and plateau pattern (Fig 6) Attempts to record a His bundle electrocardiogram failed The simultaneous pressure and intracardiac electrogram was suggestive of Ebstein s anomaly (Fig 7) Pressing the electrode catheter tip against the endocardium produced marked S T segment elevation (Fig 8)

Operative and pathologic findings The heart was quite enlarged mostly due to the huge right atrium and lacked the typical rocking motion seen in patients with Ebstein s anomaly There was no atrial septal defect or patent foramen ovale The anterior leaflet of the tricuspid valve was wide and floppy spared from extensive shrinkage thickness and distortion but the posterior and septal leaflets had downward displacement due to the traction by fibrotic tissue The entire RV cavity as well as the outflow tract was covered by a thick dense layer of fibrosis During resection of the dense right ventricular fibrotic layer the interventricular septum was ruptured and repaired The tricuspid valve was replaced by a porcine prosthetic valve The patient did not do well after the operation and died because of low cardiac output syndrome mostly due to intractable right sided failure At autopsy the left side of the heart al o was li htly involved (Fig 9)

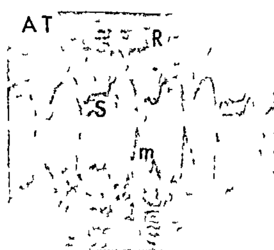


Fig 3 Mitral echogram of patient A T showing markedly paradoxical septal motion

Comments

The incidence of pure right sided endomyocardial fibrosis is not clearly known and has been reported in different articles [3] in 10% to about 50% of patients suffering from endomyocardial fibrosis

On the right side the process may be more massive than in the left ventricle and may obliterate most of the right ventricle but it still usually spares the infundibulum and pulmonary valve although the infundibulum was involved in our case

Clinical consideration When endomyocardial fibrosis involves the papillary muscle chorda and leaflets of the tricuspid valve tricuspid incompetence is common often with a huge a[4] even aneurysmal dilatation of the right atrium.

Right sided endomyocardial fibrosis has a slowly progressive course leading to right sided congestive heart failure in contrast to left sided c the combined form of the disease which rapidly leads to a fatal outcome [5] The onset of symptoms is quite insidious causing effort intolerance secondary to low cardiac output mild cyanosis peripheral edema hepatomegaly and ascites Small varicosities may be seen over the legs mostly around the ankles due to long stand high venous pressure

The following clinical findings which were present in our patient are classically mentioned in Ebstein s anomaly[6]

1 An unusual facial coloration is occasionally present resulting in a red cheeked or violaceous appearance

Case reports

Right ventricular endomyocardial fibrosis simulating Ebstein s anomaly

Massoud Alipour M D F R C P(C) F A C C
Cyavoush Tarbiat M D**
Iraj Nazarian M D***
Tehran Iran

Clinical features and the usual laboratory data as well as cardiac catheterization findings may fail to differentiate right ventricular endomyocardial fibrosis (RVEF) from Ebstein s anomaly

Since RVEF is correctable by surgery at least potentially differentiation of these ca e from Ebstein s anomaly is important and the latter also may require surgical intervention

Accurate bedside diagnosis of RVEF is some times possible however tricuspid regurgitation occasionally associated with a tricuspid diastolic flow may be confused with rheumatic heart disease[1]

This report is concerned with a case of RVEF which was operated on with a preoperative diag nosis of Ebstein s anomaly

Case History

A. T a 20-year-old man was admitted in January 19 5 with a six year history of exertional dyspnea, progressi e swelling of the face and abdomen slight bilateral ankle edema with smal varicose veins and moderate mucocutaneous cyanosis

There was neither history of rheumatic fever during child hood nor cyanosis at birth Conjunctivae and oral mucosa were congested jugular veins were engorged and the top of the venous column was seen at mandibular angle at 45 degree trunk ele ation without prominent pulsation Pulses were of low volume and blood pressure was 100/ 0 mm Hg The patient was afebrile Kussmaul s sign and paradoxical pulse were absent

From th Di is ns of Adult Cardi l gy Card o ascular Surg y and P th logy Heart Hospital Tehra Iran

Recei ed f r public ti n M y 31 19 9
Accepted f r publi ati n June 29 19 9

Reprint req sts M S Alipour M.D Di is on f Adult Cardi logy Heart Hospital Mosadegh Road T hran, I n
Di isi n of Adult Ca d ology H art Hosp tal
Di ision of Card ascula Surgery H art Hospital
Di ision f Patholog Heart Hospit l

The precordium was quiet The first heart sound was widely plit with very prominent second component A soft pansys-tolic murmur was initially heard at the patient s first physical examination at the right lower sternal border which was accentuated by in piration At his second admission in 1977 when his congestive heart failure was severe this murmur could hardly be heard without any change in in piration Right ventricular gallop was present at both admissions. A and P were phy iologically split and were normal in inten i ty

A few bilateral basal crepitant rales were present initially which cleared soon following digoxin and diuretic therapy A moderate amount of ascites was present The liver was enlarged 4 cm below the ri ht costal margin

Hepatic systolic pulsation which was present at his first admission in 19 5 was not felt at the second admission and it was thou ht that the liver was slightly maller

Slight pitting edema and many small varicose vein were observed mostly around the ankles Moderate clubbing was present

Electrocard ogram and chest roentgenogram The electro-cardiogram showed atrial fibrillation and a pattern of incom pelete right bundle branch block (RBBB) (Fi 1) A chest x ray revealed an enlarged balloon shaped heart with a very prominent right atrium and a narrow vascular pedicle The enormous cardiac shadow contrasted with oligemia of the lung fields (Fig 2)

Echocardiogram The first echocardiogram was interpreted as simultaneous tricu pid and mitral valve echograms Two leaflets of the tricu pid valve could be seen during the entire cardiac cycle simulating a pattern of tricuspid stenosis The time difference between the mitral and tricuspid closure was too long almost half a cardiac cycle Scanning from the aorta to the mitral area revealed normal aorto-mitral continuity and the anterior wall of the aorta was in continuation with what we thought was the tricuspid valve (Figs. 3 and 4)

Catheterizat on data and intraca d ac electroca d ogram Catheter manipulation did not induce significant arrhyth mias Atrial septal defect or patent foramen ovale was not found Entering the right ventricle and pulmonary artery was not easy Leftward displacement of the tricuspid valve was noted during angiography and pressure curve recording (Fig 5) Arterial oxygen saturation was low (8) Mean ri ht atrial pressure was high (24 mm. Hg) Right ventricular

0002-8 03/80/1 0859 + 0 $00 0/0 © 1980 The C V Mosby Co

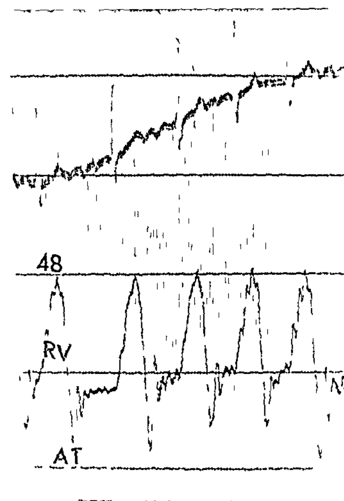


Fig 6 A right ventricular pressure curve illustrates a dip and plateau pattern and high end diastolic pressure

Conduction disturbances were seen in 19 of the 95 cases reviewed by Ratzner and co workers Bundle branch block and intraventricular conduction delays were the most frequent occurrences not surprising in view of the endomyocardial thick fibrotic lesion In endomyocardial fibrosis unlike fibroelastosis the normal layers of the endocardium are destroyed and are replaced by thick scar tissue although only one patient out of 21 patients reviewed showed the pattern of incompelete RBBB This is in contrast to Ebstein s anomaly in which 75% to 80% of these patients have a complete or incompelete RBBB although this is considered atypical because of the low voltage and polyphasic configuration and it has no specific or diagnostic feature

Echocardiography Simultaneous recording of the tricuspid and mitral valve echograms is not unusual in Ebstein s anomaly Decreased tricuspid diastolic closure slope (E F slope) is one of the echocardiographic features of this anomaly although the amplitude of what was thought to be two leaflets of the tricuspid valve was less than mitral valve motion and this is not the case in Ebstein s malformation According to Lundstrom [13] an echo from the posterior or septal tricuspid leaflet is rarely recorded in Ebstein s anomaly Delayed tricuspid closure is considered to be the most consistent echocardiographic feature of the abnormally positioned tricuspid valve but its continuation with the anterior wall of the aorta cast doubt on our previous belief and apparently this was the interventricular septum with markedly exaggerated paradoxical motion (Fig 3) Although it is said that all patients with Ebstein s malformation have type B septal motion (the septal echoes become flattened during systole instead of anterior motion in type A) five out of 19 patients reported by Lundstrom had type A septal motion Therefore Ebstein s anomaly could not be ruled out by this finding

Interpretation of catheterization data and electrophysiological studies

Leftward displacement of the tricuspid valve has been considered a valuable sign in Ebstein s anomaly and this was also apparent in our patient The apex of the right ventricle (RV) was obliterated by scar tissue and the RV cavity was shrunk and contracted This was confirmed by RV angiography, which showed the absence of the usual apical cavity initially thought to be the RV proper of Ebstein s anomaly (Fig 5)

Atrial septal defect or patent foramen ovale which was present in 14 out of 65 cases with Ebstein s anomaly, was not found.[1] In a report by Kumar and associates [5] seven out of 55 patients with Ebstein s malformation developed transient tachycardia this did not happen in our patient Difficulty in entering the RV and pulmonary artery [1] low arterial O saturation and high mean right atrial and RV end diastolic pressure may be encountered in both entities. The RV pressure curve had a dip and plateau pattern simulating constrictive pericarditis but this may be seen in chronic right sided disease pericardial effusion primary pulmonary hypertension and with intracardiac tumor [1, 11] This appearance could be due to deep intramyocardial penetration of the fibrotic process causing an early diastolic

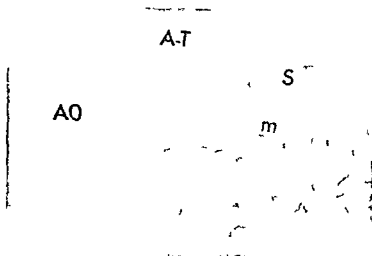


Fig 4 Echogram of the patient showing aorto mitral continuity

2 The relatively unimpressive jugular venous pulsations present because of the huge right atrium and the toneless atrialized right ventricle

3 Absence of a systolic impulse over the body of the right ventricle

4 Early systolic murmurs in Ebstein s anomaly generally do not increase during inspiration despite their tricuspid origin

In reviewing 10 patients with Ebstein s anomaly Crew and associates have found that the only constant anomaly was abnormally wide splitting of the first sound with accentuation of the delayed component This abnormal sound was thought to be caused by delayed closure of the abnormally large anterior leaflet of the tricuspid valve The intensity of the sound despite a hypodynamic right ventricle is of interest in relation to the mechanism of heart sounds

According to Fontana and colleagues the systolic sound may not be a closure sound since it is present in cases with considerable tricuspid regurgitation where the leaflets may not approximate at all The sound is probably more related to the termination of motion of the anterior leaflet which was larger than usual in our patient

Electrocardiography In studying the electrocardiographic findings in 30 case of endomyocardial fibrosis[a] no specific diagnostic pattern was found except for an abnormal P wave (P mitrale or pulmonale) a low voltage QRS and nonspecific changes in T waves

Atrial flutter or fibrillation are seen in only 2% to 5% of patients with Ebstein s anomaly while

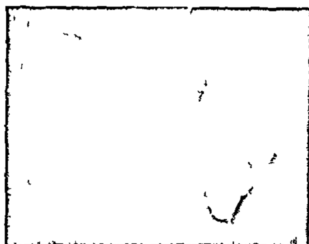


Fig 5 Right ventricular angiogram shows leftward displacement of the tricuspid valve with a dilated right atrium

six of 11 patients with endomyocardial fibrosis had this rhythm Our patient had both atrial fibrillation and a pattern of incompelete right bundle branch block (Fig 1)

Although our patient did not have episodes of supraventricular tachyarrhythmias which are well known in Ebstein s anomaly a high incidence of arrhythmias is reported in endocardial fibroelastosis probably due to degenerative changes in the cells of the cardiac ganglia We are not aware of this histologic change in endomyocardial fibrosis The absence of supraventricular tachyarrhythmias in our patient could be due to atrial fibrillation which is rare in Ebstein s anomaly and is rather common in endomyocardial fibrosis

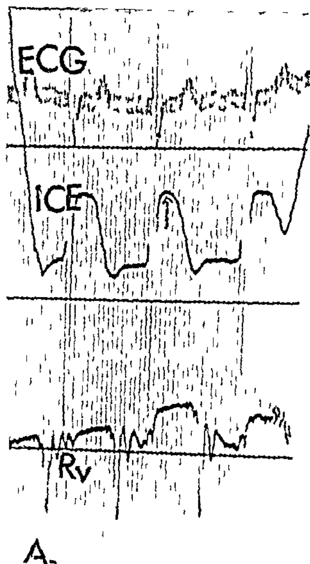


Fig 8 Intracardiac electrogram recorded while pressing the electrode catheter tip against the right ventricular endocardium damping the pressure and producing a contact potential (arrow)



Fig 9 At autopsy a thick layer of right ventricular endomyocardial fibrosis was found

retrospect was considered to be probably due to a thick layer of fibrosis covering the septal surface of the right ventricle

Conclusion

A differential diagnosis between these two rare entities which require different therapeutic approaches is important The reported results of surgical treatment of RVEF are encouraging while in Ebstein s anomaly this is not the case and one should be more conservative in sending patients for operation Clinical features and chest roentgenograms could be quite similar and electrophysiologic studies may be misleading Cineangiograms rather than rapid sequence films seem to be very reliable for this differentiation

Summary

A case of right ventricular endomyocardial fibrosis simulating Ebstein s anomaly is described The clinical features chest x ray electrocardiogram echocardiogram intracardiac electrogram and the angiogram were all compatible with Ebstein s malformation A correct diagnosis was subsequently made in the operating room Reasons for the difficulties in the differential diagnoses of these two entities are discussed

We wish to thank Dr Jamu Shakibi for his advice in the preparation of this manuscript and Dr Harvey Feigenbaum for interpreting the echocardiogram

REFERENCES

1 Falase A O Kolawole T M and Lagundoye S B Endomyocardial fibrosis Problems in differential diagnosis Br Heart J 38 369 1976

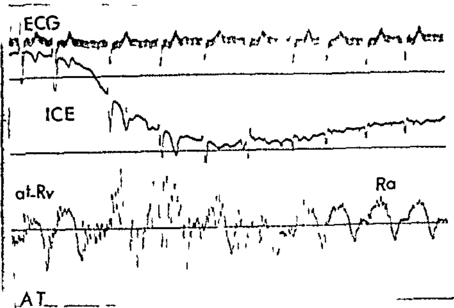


Fig 7 Simultaneous intracardiac electrogram *(ICE)* and pressure recording An intracavitary potential is recorded immediately after withdrawing the catheter from the right ventricle presumably into the atrialized right ventricle *(at RV)*

recoil after termination of RV contraction (Fig 6) In severe RVEF the right ventricular apex is mostly obliterated and the infundibulum is dilated with tricuspid regurgitation pressure pulses from the pulmonary artery the RV and the right atrium are distorted and resemble each other This entity could be quite similar to Ebstein s anomaly when the pressure curves are identical In our case the pressure curves were similar but not identical (Fig 7) Therefore local ization of the catheter tip by pressure pulse could be inaccurate It is known that when an electrode catheter touches the normal endocardium there will be an S T segment elevation which is called "contact potential rather than current of inju ry [9] Some authors believe that this contact potential may be almost absent or minimal when the electrode touches the area which is covered by a thick layer of endocardial fibrosis Significant S T elevation was present in our right ventricular intracardiac electrocardiogram in spite of a dif fuse and thick layer of RV endomyocardial fibro sis (Fig 8) Probably by repeated catheter manip ulation and positioning we could also get right ventricular pressure and ECG pattern without S T elevation According to Sodi Pallares this contact potential should be recorded when the atrialized right ventricle is also touched by the catheter tip whereas contact with the true atrial endocardium should produce elevation of the P Q segment Although S T segment elevation was produced in only one out of eight patients studied by Lowe and co workers this change was clearly shown in our patient Upon withdrawing the catheter when the pressure dropped and the pressure curve changed slightly hand injection of dye proved that the catheter tip was out of the RV In this position the QRS voltage decreased markedly but a ventricular pattern (rs) remained There was no S T segment elevation (Fig 7)

Watson[18] has mentioned many pitfalls in intra cardiac electrocardiography and the reasons for having false positive and false negative diagnoses of Ebstein s malformation It has been demon strated that a normal intracardiac electrocardio graphic and pressure relationship might be pres ent when the catheter is withdrawn across the anterior ricuspid leaflet or true annulus at the midatrial level When the right ventricular cavi ty is obliterated or contracted due to RVEF the difference in the magnitude as well as the direc tion of the unbalanced electrical forces on two sides of the high ventricular septum may cause an electrode catheter to continue to record ventricu lar potentials after it entered the right atrium

Failure to record His bundle deflection in

Congenital pericardial defect associated with cardiac incarceration: Case report

Reiko Saito
Futsumi Hotta
Tokyo, Japan

A congenital defect of the pericardium is rare. Since Columbus reported the first case in 1559,[1] only around a hundred cases have been found in the whole world. Though such symptoms as palpitation and exertional chest pain occasionally occur, the overwhelming majority of the patients remain asymptomatic, and the defect is discovered by chance in a postmortem examination or operation.

A young child with the congenital pericardial defect who died of incarceration of the left ventricle was seen at the Tokyo Medical College Hospital. The clinical course and autopsy findings are described below.

Case report

This 4 year old boy had been healthy since birth. In the evening of April 19, 1979, he had a fight with his 7 year-old sister over a book and accidentally struck his chest with his own fist. Chest pain started immediately after this episode which was agonizing and was accompanied by gradually increasing facial pallor. He was admitted to a nearby hospital 30 minutes after the accident. Chief findings on admission were as follows: ... n iousness lethargic, respiration rate 44/minute, pulse rate 1?6/minute, blood pressure 98/66 mm H..., body temperature 3.. ... C, ... s t lic murmur over the apex and the liver palpable for ... m. Peripheral blood count showed a neutrophilia (whc ...,800 and ...% neutrophils). ECG recording taken immediately after admission showed a strong right axis d... ... ... ation of the ST segment as we... ... ... in Leads II, III and aV..., from which ... ... the inferior wall through the apex ... ... A chest x-ray disclosed de...ati... ... the h...ar... ... ... n, left abnormal protrusion of the left third and fourth arch, and ... ... lung marking (Fig. 2, *left*).

After admission, chest pain persisted, the ... became worse, and the patient sometimes cried ... Systolic blood pressure fell to 64 mm Hg. Oxygen ther..., adrenocortical hormones, cardiotonics, and ... ... bonate solution were used. Twelve hours after onset the p... was 110/minute, irregular and faint, while the ... cyanotic. ECG recordings taken 13 hours after onset showed that the ST segment, contrary to the previous ..., ... depressed in Leads II, III, and aV..., and was elevated in Leads I, aV$_L$, and V... to V..., which suggested ischemia centering in the lateral wall (Fig. 1B). The patient was referred to our hosp... at 2 P.M. on April 20, 1979, at which time consciousness ... lethargic, measurement of blood pressure was not ..., pulse rate was 80/min., respiration rate was .../min, and ... generalized cyanosis as well as edema of the face and ... were noted. Chest x-ray revealed more marked protrusion of the left third and fourth arch (Fig. 2, *right*). The patient died ... minutes after admission, 19 hours after onset.

Gross findings at autopsy were as follows: A tumor of ... egg size was observed on the left side of the heart on ope... the chest which, when the heart was removed, was ... to be the left ventricular wall protruding through the ... created by a partial defect of the pericardium (3.5 x 4.5 cm ...) that is, the left ventricle was incarcerated. The ... wall at the borders of the incarceration was squeezed ... presented a picture of a clear deep entrapment, ... posterior wall. The incarcerated part was clearly differ... from the normal part in color tone. The part ... incarceration included the apex, the posterior and lateral ... and a portion of the anterior wall of the left ventricle (Fig. 1 ... and B).

Besides the aforementioned abnormalities, ... ml of ... fluid was accumulated only in the left thoracic ca... and ... liver and lung were congested.

Histopathologically, the peripheries of the pericardial de... were marked by conspicuous thickening of the ... pericardium and by an increase in collagen fibers (Fig. 4) ... myocardium in the incarcerated part was marked ... in general and showed congestion and hemorrhage ... necrosis here and there besides being infiltrated ... cytes. Myocardial necrosis was more conspicuous on ... anterior than on the posterior wall. Around the ... part, myocardial infarction was more severe than ... healthy part (Fig. 5).

From the Departmen... ... Tok... Med... ...lle...e Hospital, Tokyo, Japan.

Received for publicat... M...
Accepted for publicatio...

Reprint requests: Dr. Re... Tokyo Medical College Hospital, 6- 1 Ne... ...n

...-8703/80/120-66 + 0$00.50/0 © 1980 The C. V. Mosby Co.

Brockington I F and Olsen E G J Loffler s endocarditis and Davies endomvocardial fibrosis AM HEART J 85 308 19/3
3 Cockshott W P Saric S and Ikeme A C Radiological findings in endomyocardial fibrosis Circulation 35 913 1967
4 Emslie Smith D and Somers K Intracardiac electro cardiogram in endomyocardial fibrosis Br Heart J 30 696 1968
5 Dubost C H Maurice P Gerbaux A et al The surgical treatment of constrictive fibrous endocarditis Ann Surg 184 303 1976
6 Perloff J K The clinical recognition of congenital heart disease Philadelphia 1970 W B Saunders Company p 13
7 Crew T L Pridie B R Benham R et al Auscultatory and phonocardiographic findings in Ebstein s anomaly Br Heart J 34 681 1972
8 Fontana M E and Wooley C F Sail sound in Ebstein s anomaly of the tricuspid valve Circulation 36 155 1972
9 Williams A W and Somers K The electrocardiogram in endomyocardial fibrosi Br Heart J 30 311 1960
Lowe G Emslie Smith D Robertson P G C et al Scalar vector and intracardiac electrocardiograms in Ebstein s anomaly Br Heart J 30 617 1968
Zoltowaska A Endocardial fibroelastosis in children with special reference to the lesion of cardiac ganglia J Clin Pathol 24 ?63 1971
12 Raizner A E Silverman M E and Waters W C Conduction disturbances and pacemaker failure in Loffler s endomvocarditis Am J Med 53 353 1972
13 Lundstrom N R Echocardiography in the diagnosis of Ebstein s anomaly of the tricuspid valve Circulation 47 597 1973
14 Bialostozky D Horwitz S and Espino Vela J Ebstein s malformation of the tricuspid valve A review of 65 cases Am J Cardiol 29 826 1972
15 Kumar A E Fyler D C Miettinen O S et al Ebstein s anomaly Am J Cardiol 28 84 1971
16 Somers K Brenton D P Arbela P et al Hemodynamic features of severe endomyocardial fibrosis of the right ventricle including comparison with constrictive pericarditis Br Heart J 30 322 1968
17 Davie H Deuchar D and Missen G A Endomyocardial fibrosis Two cases of severe pulmonary hypertension presenting in England Guy Hosp Rep 114 337 1965
18 Watson H Electrode catheters and the diagnosis of Ebstein s anomaly Br Heart J 28 161 1966
19 Sodi Pallares D and Marisco F Importance of electrocardiographic patterns in congenital heart disease AM HEART J 49 202 1955

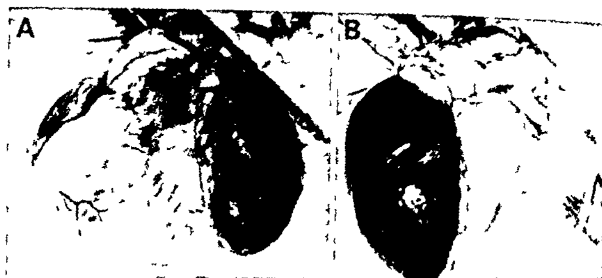


Fig 3 Autopsy findings *A* Frontal aspect of the resected heart the incarcerated left ventricle is seen as a dark mass on the right side *B* Posterior aspect of the resected heart the incarcerated left ventricle is seen as a dark mass on the left side Distension of the coronary vein is clear

Table I Reported cases of death due to cardiac incarceration in congenital pericardial defect

Author	*Nationality*	*Year*	*Age of patient*	*Sex*	*Site*	*Time betwe onset & d*
1 Boxall	–	188[illegible]	28 yrs	F	Apex	30 hr
2 Sunderland	Australia	1944	2 yrs	M	Left ventricle	11 hr
3 Bruning	South Africa	1961	[illegible] yrs	F	Apex	19 hr
4 Present authors	Japan	1979	4 yrs	M	Left ventricle	19 hr

Subjective symptoms are rare with either type of the defect In the left extensive defect however absence of the support for the left sided heart sometimes leads to such complaints as palpitation sensation of throbbing heart and chest pain at the time of exertion and the heart is frequently found to be deviated to the left on x ray examination The left partial defect is sometimes discovered from an abnormal shadow in the chest (protrusion of the left second arch) due to deviation of the left atrium Very rarely the left atrium and left ventricle protrude through the partial defect and the patient dies from incarceration Robin and associates reported their successful life saving surgery for incarceration of the left atrium that was discovered while performing emergency surgery for sudden shock in a 28 year old man with the left partial pericardial defect If a part of the left ventricle is incarcerated through the defect the coronary artery is compressed, with resultant myocardial infarct and death The aforesaid accident is extrem rare and so far has been found only in three ca in the literature including one reported Boxall in 1887[5] Onset was sudden and de occurred in a relatively short time in all th cases (Table I)

In the present case the pericardial defect w located in the region of the left ventricle and w large enough to permit protrusion of the l ventricle which constituted the primary fac for incarceration of the left ventricle Histolo cally the inner side of the borders of the perica dial defect was thickened and a flap like p dial defect was thickened and a flap like pe between the outer and the inner side was sca tered with fat while the outer membrane co tained markedly fibrotic small vessel here there The above changes suggest that a mech ical stress had been applied to the said tissue f long time The left ventricular wall showed a de

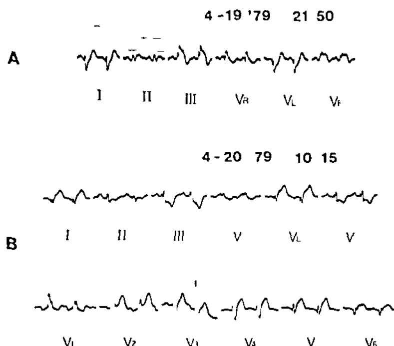


Fig 1 *A* ECG on admission Right axis deviation elevation of the ST segment and inversion of the T wave in Leads II III and aV *B* ECG recordings taken 13 hours after onset Depression of the ST segment in Leads II III and aV and elevation of the ST segment in Leads I aV and V to V

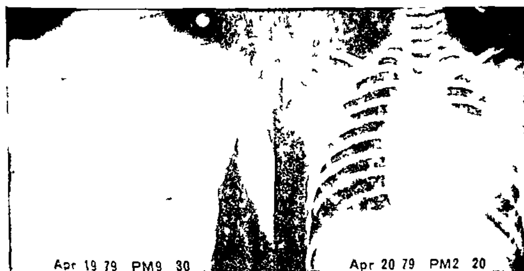


Fig 2 Chest x ray *Left* one hour after onset *Right* 18 hours after onset There is deviation of the heart shadow to the left abnormal protrusion of the third and fourth aortic arches, and intensification of the lung marking

Discussion

Congenital pericardial defect is a relatively rare congenital anomaly originating in agenesis of the pericardium and parietal pleura According to Perna a defect of the pericardium and pleura results if the left common cardiac vein (Cuvier s duct) atrophies early around the eighth embryonic week since nutrition of the pleuropericardial membrane separating the pleural and the pericardial cavity is disturbed by such an early obliteration Because the right Cuvier s duct remains as the superior vena cava this anomaly is usually found on the left side It may be extensive or partial depending upon the size of the defect

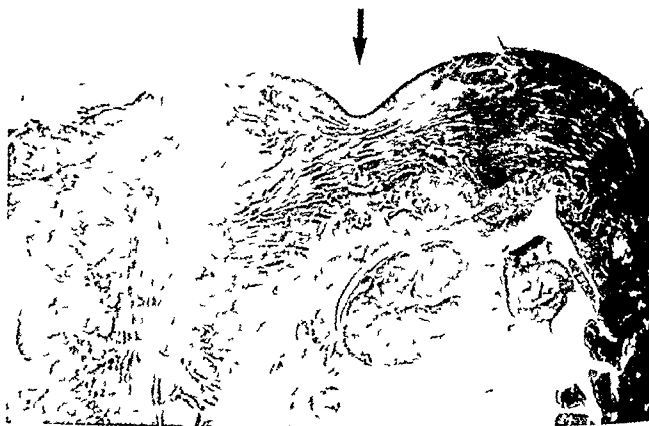


Fig 5 Histological view of the myocardium of the left ventricle *Left* normal *Right* the incarcerated part that shows hemorrhage and necrosis *The arrow* shows the impression produced by the border of the pericardial defect

through fixing of the heart with the use of Teflon mesh These surgical treatments however must be preceded by preoperative diagnosis for which the aforesaid diagnostic procedures are useful

Summary

1 A 4 year old boy with the congenital partial defect of the left pericardium who presented with myocardial infarction died of incarceration of the left ventricle

2 This is the fourth reported case of death from this anomaly in the world

3 Because this anomaly occasionally causes sudden death it is important to diagnose the condition while the patient is alive

We are deeply grateful to Prof Teruo Honda for reviewing the manuscript Our sincere gratitude is also expressed to Dr Shigeru Masuda of the First Pathology Laboratory of Tokyo Medical College Dr Ryozo Okada of Juntendo University as well as Dr Nobuk Yanagisawa and Dr Takashi Wada of Kokusai Shinzen H for their kind advice

REFERENCES

1 Columbus R De re anatomica 1o,2f3 1559
2 Saito K Matsuhisa M Fukuda N Nishioka ... Niki T A case of the congenital partial absence of the left pleuropericardium—especially the findings of the jugular venous pulse (in Japanese) Kokyu to Junkan 27 425 1979
3 Perna G Sopra un arresto di sviluppo della ... pericardica nell uomo Anat Anz 35 323 1909
4 Robin E Ganguly S and Fowler M Strangulation of the left atrial appendage through a congenital partial pericardial defect Chest 67 354 1975
5 Boxall R Incomplete pericardial sac escape of heart into left pleural cavity Trans Obstet Soc 28 ... 1887
6 Sunderland S and Wright Smith R Congenital pericardial defects Br Heart J 6 167 1944
7 Bruning E Congenital defect of the pericardium J Clin Pathol 15 133 1962
8 Yanagisawa N Honda M Tarumi K Higuchi ... Wada T Non invasive diagnosis of pleuro-pericardial defect (in Japanese) J Cardiography 9 1?9 1979
9 Kubo K Ishikawa O Kusakawa M Shomura T Namikawa S Fukumori S and Yoshioka M Congenital deficiency of the pericardium and its clinical meanings (in Japanese) Nippon Kyobu Geka Gakkai Zasshi 13 8 840 1965

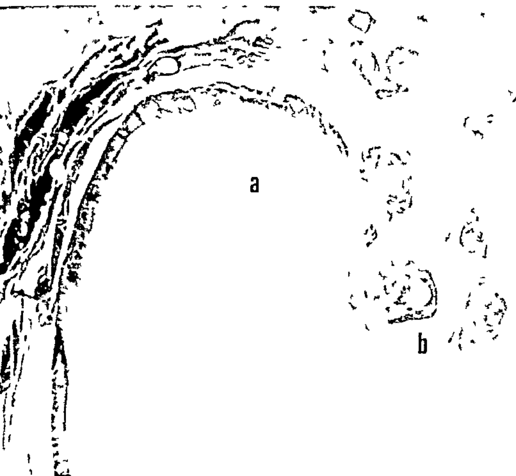


Fig 4 Peripheries of the pericardial defect a hows thickening of the inner layer b shows marked fibrosis of the outer membrane of small vessels in the flap like portion

sion produced by a ligament on the poste le from which that part of the ventricular as considered to have repeatedly passed h the pericardial defect to protrude or ack for a considerably long time Applica an external force to the chest in the form tusion was considered to have precipitated versible protrusion of the ventricular wall ch ischemia of the inferior and posterior of the left ventricle occurred first then s return was inhibited as the anterior wall ushed outside in turn and congestion rhage and decrease in arterial flow ensued t order with the resultant severe cardiac and death

recordings showed elevation of the ST nt in Leads II III and aV_F immediately admission and marked elevation of the ST nt in Leads I aV_L and V to V 13 hours that The aforesaid changes in the ECG st that myocardial necrosis progressed from the lateral to the anterior wall This finding agreed with the histological findings

In the present case a systolic murmur was heard after the occurrence of incarceration This heart murmur seemed to have resulted from functional failure of the papillary muscle due to myocardial necrosis and subsequent mitral insufficiency In all the previously reported cases of death from cardiac incarceration mentioned above a systolic murmur was noted

Since sudden death occasionally occurs with the congenital pericardial defect it is important to diagnose the condition while the patient is alive Diagnosis is generally made by chest x ray ECG echocardiography and artificial pneumothorax A jugular phlebogram is helpful as a safe test causing little pain

The treatment of the congenital pericardial defect consists of closure of the defect by direct suture or fixing of the heart Kubo and colleagues reported that they obtained good results

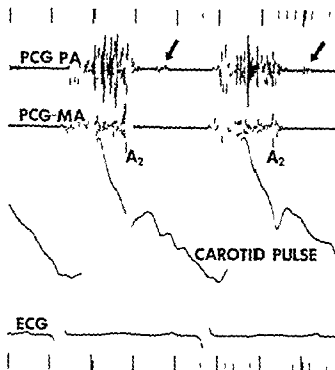


Fig 1 Phonocardiogram of pulmonary area *(PCG PA)* and mitral area *(PCG MA)* A harsh systolic murmur and a diastolic sound *(arrow)* were recorded The murmur continued beyond the aortic component of the second heart sound *(A_2)* and the sound was separated approximately 150 msec from A Time intervals equal 40 msec

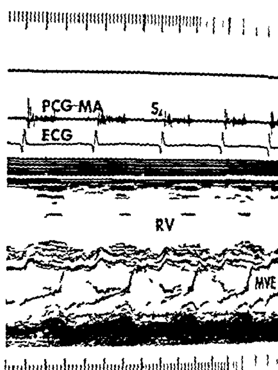


Fig 2 Echophonocardiogram showing the dilatation of the right ventricle *(RV)* The interventricular septum is abnormal in that it moves anteriorly in early systole *MVE* = mitral valve echogram Vertical distance between dots is 1 cm S_4 = fourth heart sound.

the tricuspid orifice to the right atrium Pulmonary regurgitation was noted During levophase the left side of the heart was normal. There was no intracardiac shunt

Operative findings Surgery performed with the diagnosis of right ventricular tumor A palpable thrill during systole was present over the right ventricular outflow tract A transverse right outflow tract incision was made exposing the pedunculated intracavitary tumor The tumor was 6 × 3 × 2.5 cm in size and 27 g in weight (Fig 6) It was easily delivered from the pulmonary artery through the pulmonary valve which appeared to be normal The attachment was entirely excised including the full thickness of the anterior right ventricular wall The pathological diagnosis was myxoma The patient had an uneventful recovery

In a postoperative echophonocardiogram the tumor echoes were no longer visible in the right ventricular outflow tract The right ventricular dimension was still increased, but a normal pulmonary valve was recorded No adventitious systolic or diastolic sounds were recorded

Angiographic analysis In order to investigate the relationship between the motion of the tumor and the diastolic sound we traced frame by frame the configuration of the tumor provided by cineangiography (Fig 7) In mid-diastole the tumor fell back into the ventricle and reached its most anterior and inferior position where it could be seen to strike the right ventricle in the lateral angiographic views (arrow in Fig 7) In presystole when the right ventricle remained dilated atrial contraction forced the tumor upwards, toward the pulmonary valve and with the subsequent ventricular contraction part of the tumor was propelled through the valve retaining this advanced position throughout systole The pulmonary valve could not be seen clearly through the cardiac cycle but in diastole the tumor mass was clearly located below the valve

Discussion

Myxoma of the right ventricle is extremely rare compared to its occurrence in the right or left atrium We could find only 33 reported cases in the literature[3] [4] These consisted of 18 males and 15 females with ages of 2 months to 65 years averaging 26.8 years Clinical findings as well as physical manifestations are mainly dependent on the position and size of the tumor within the right ventricle Most myxomas are movable or pedunculated and sometimes have a long stalk except for one adult case[5] and two infant cases in which the tumor cells infiltrated the myocardium Right ventricular myxomas usually originate in the free wall or in the interventricular septum and in some cases in the tricuspid valve the pulmonary ring[6] or the valve

Right ventricular myxoma Case report and review of phonocardiographic and auscultatory manifestations

Yoshiyuki Hada M D
Carla Wolfe
Gordon F Murray M D
Ernest Craige M D
Chapel Hill N C

Tumors of the right ventricle are extremely uncommon We recently observed a patient with a right ventricular myxoma whose physical find ings included a peculiar sound in mid diastole The purpose of this case report is to describe the pathogenesis of this vibration a tumor plop as determined by combined echo and phonocardio graphic studies supplemented by cineangiogra phy Previously reported cases are reviewed with special reference to phonocardiographic and aus cultatory findings

Case Report

A 28-year old man was admitted to North Carolina Memo rial Hospital for evaluation of a heart murmur The patient had been in good health until two years previously At that time he noticed a pressure" feeling in his chest when he lifted moderately heavy objects or climbed stairs He also noted palpitations and shortness of breath He had no diaphoresis, nausea or pain He had a history of having been athletically inclined and instituted a program of weight control and physical conditioning in order to overcome his symptoms. He lost 20 pounds from 190 to 170 but was unable to diminish the palpitations and dyspnea In June 1979 when he was jogging as he had done on many occasions he had a sudden dizziness followed by syncope of brief duration This was accompanied by palpitation and a flushed feeling with dyspnea He con sulted a local physician who noticed a heart murmur and referred him to our hospital The patient had no history of rheumatic fever frequent respiratory infections, or cyanosis. Past and family history were unremarkable

On physical examination the patient was of athletic build His blood pressure was 121/98 mm. Hg pulse 76/minute and regular respiration 16/minute and temperature was 98 9 F The jugular pulse showed a prominent a" wave Carotid arterial pulse had a normal upstroke without thrill. There was no heave or thrust of left or right sided ventricular enlarge ment The first heart sound wa normal There was a harsh, grade 4 systolic murmur with a thrill in the second intercostal space The murmur did not vary in intensity with respiration An additional sound was audible in mid-diastole

His chest roentgenogram showed mild cardiomegaly with out specific right ventricular enlargement or poststenotic dilatation of the pulmonary artery The pulmonary vascular pattern appeared normal The ECG revealed normal sinus rhythm and relatively prominent R waves with ST T abnor malities in Leads V and V suggestive of right ventricular strain The phonocardiograms (Figs 1 and 2) confirmed the auscultatory findings and in addition demonstrated an atrial sound (S) of low intensity In the second left intercostal space a dia tolic sound was recorded (arrow in Fig 1) 150 msec. after A

A conventional echocardiogram with transducer directed across the interventricular septum showed a dilated right ventricle (Fig 2) With the transducer angulated posteriorly and superiorly in the optimal direction for visualization of the pulmonary valve a dense mass was seen moving posteriorly with ventricular systole and anteriorly in diastole (T in Figs 3 and 4) Combined echophonocardiography showed that the point of apparent contact of this mass with the anterior wall of the right ventricle coincided with the first vibration of the diastolic sound noted above (Fig 4)

Right heart catheterization showed a mean right atrial pressure of 7 mm Hg right ventricular pressure of 100/10 mm Hg and pulmonary pressure of 15/7 mm Hg The right ventriculogram demonstrated a dilated right ventricle A large well circumscribed lobulated filling defect was noted in the outflow tract of the right ventricle prolapsing partially through the pulmonary valve with each contraction (Fig 5) The tumor was not attached to the pulmonary valve and did not appear to involve the tricuspid valve nor herniate through

From the D partm nt of Medic (Cardiology) nd Surgery of Th University of North Carolina School of Medicin and Th C V Richardson Laborat ry of th N rth Carolina Memorial Hosp tal Chapel Hill N C

Recei ed f r p blication March 17 1980
Accepted f r publication Ap 16 1980

Reprint requests Ernest Craig M D 338 Clini al S iences Building 229H, UNC School of Medicin Ch pel Hill, NC 27514

0002-8 03/80/120871 + 0,$00 0/0 © 1980 The C V Mosby Co

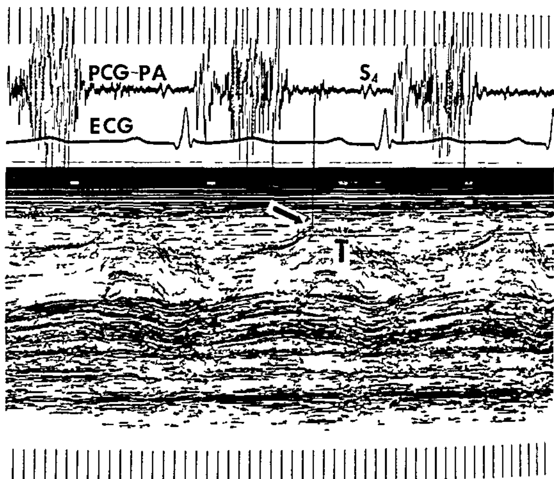


Fig 4 A high speed recording (100 mm./sec) of echophonocardiogram showing the relationship between the tumor motion and diastolic sound In mid-diastole the tumor *(T)* is observed to strike the right ventricular wall *(arrow)* and to induce diastolic vibrations With atrial contraction preceding ventricular ejection the tumor moved posteriorly This probably reflects the reverse pressure gradient across the tumor in presystole as demonstrated by catheterization



Fig 5 Lateral view of cineangiogram demonstrating the mass in the right ventricular outflow tract *(arrow)*

loud [4, 33] An ejection sound was present in six cases [13, 0, 5, 9, 34] However none of the reported cases had pulmonary valvular stenosis An opening snap was heard in one case with obstruction of the tricuspid orifice [33]

The pulmonic component of the second heart sound (P_2) and the diastolic sound or murmur are noteworthy but were not mentioned in detail in most of the reports S_2 in cases with pulmonary obstruction was variable—widely split and accentuated [3] narrowly split or normal [1]

Diastolic murmurs were described in 11 cases There were three cases with tricuspid rumble due to tricuspid obstruction or regurgitation as mentioned before and four with pulmonary regurgitation [7, 1, 28, 34] Two cases with pulmonary regurgitation had a perforated pulmonary valve and in another case surgical replacement of the valve was performed [1]

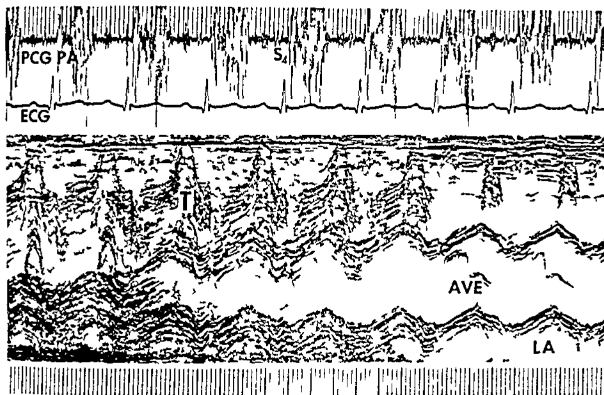


Fig 3 Scanning echocardiogram from the right ventricular outflow tract to the aortic valve *(AVE)* The dense echo of the tumor *(T)* is noted to move forward and backward with each heart beat in the outflow tract *LA* = left atrium

They tend to extend toward the right ventricular outflow tract or even prolapse through the pulmonary valve along with the blood flow in systole Therefore typical cases present clinical findings consistent with pulmonary steno sis—symptoms of dyspnea and syncope with ejec tion systolic murmurs Some cases with atypical findings have however been reported In a rare instance there have been no symptoms In oth ers there have been heart failure without pulmo nary obstruction [2] [33] endocarditis involving the pulmonary valve [16] [28] [34] atrial septal defect [4] pulmonary embolism [2] bronchitis [9] and hemopty sis [1] The duration of symptoms and clinical signs mentioned above varied from five weeks to 14 years [1] There are also familial[16] [24] [3] or recurrent cases [1] [3] reported

In our review of 33 cases there were only two patients without a systolic murmur [2] one of whom had an outflow obstruction gradient of 40 mm Hg [21] Systolic murmurs in the reported cases were initially attributed to pulmonary stenosis and only retrospectively explained by the tumor in 24 cases including three with an associated murmur of secondary tricuspid stenosis [31] or regurgitation [3] The intensity of these murmurs was variable from 2 to 6 the louder ones being associated with a palpable thrill at the upper left sternal border The pressure gradient across the tumor was from 8 to 94 mm Hg and averaged 51 8 mm Hg In one case in which the tumor filled the whole right ventricle to and for scratchy sounds were noted [19] The intensity of the murmur varied with the positional change of the body [1] or from one day to another [4] [13] The effect of respiration on the intensity of the systol ic murmur was inconsistent the murmur being decreased [29] abolished intensified [9] or not changed[13] [22] with inspiration Pan or holosystolic murmurs were present in four cases [8] [9] [1] [3] one of which had an annuloplasty of the tricuspid valve Thus the systolic murmur itself lacked specificity as a diagnostic sign for right ventricu lar myxoma

The first heart sound (S) was unremarkable in all except two patients in whom it was unusually

sents tumor plops It is unknown how often this diastolic vibration occurs in right ventricular myxoma There is a possibility that it is missed or interpreted as delayed P_2 or diastolic murmur unless a phonocardiogram preferably in conjunction with an echocardiogram is carefully recorded We believe its presence would be helpful in making the diagnosis just as with the tumor plop of left atrial myxoma which is due to antegrade movement of the tumor in diastole In conclusion a diastolic sound or short vibration which occurs 130 to 160 msec after A, should be borne in mind as one of the auscultatory findings of right ventricular myxoma in a situation in which pulmonary stenosis is suspected

Summary

Tumors in the right ventricle are extremely rare This report concerns the pathogenesis of physical signs resulting from a right ventricular myxoma In systole a loud midsystolic murmur representing outflow obstruction was present In diastole a prominent vibration was heard and recorded By echophonocardiography this noise could be ascribed to sudden halting of the retrograde excursion of the mass into the right ventricle—a mechanism analogus to the tumor plop associated with the halting of antegrade movement of a left atrial myxoma in the left ventricle in early diastole

REFERENCES

1 Prichard R W Tumor of the heart Review of the subject and report of one hundred and fifty cases Arch Pathol 51 98 1951

2 Newman H A Cordell A R and Prichard R W Intracardiac myxomas Literature review and report of six cases one successfully treated Am Surg 32 219 1966

3 Kishimoto M and Sakakibori S Primary tumor of the heart Report of a case with myxofibroma of the right ventricle Am Heart J 57 769 1959

4 Michaud P Saubier E Maret G Termet H Gravier J and Dalloz C Exérèse sous circulation extra corporelle d un myxome du ventricule droit Lyon Chir 56 788 1960

5 MacRae F R and Galea M Myxoma of the right ventricle of the heart Can Med Assoc J 85 435 1961

6 Ernst R W Siebel E K Ogle J C Chapman C B and Bashour F A Successful removal through the main pulmonary artery of a tumor arising from the ventricular septum A case report Ann Surg 156 54 1962

7 Catton R W Guntheroth W G and Reichenbach D D A myxoma of the pulmonary valve causing severe stenosis in infancy Am Heart J 66 248 1963

8 Gottsegen G Wessely J Arvay A and Temesvári A Right ventricular myxoma simulating pulmonic stenosis Circulation 27 95 1963

9 Doohen D J Greer J W Diono N and Timmes J J Emergency excision of a myxoma of the right ventricle which was obstructing the right ventricular outflow tract J Thorac Cardiovasc Sur 47 347 1964

10 Crummy A B and Hipona F A The radiologic aspects of right ventricular myxoma Br J Radiol 37 ... 1964

11 Dalloz C Agé C and Cahen P A propos d un cas de myxome du ventricule droit suspecte au cathétérisme droit Arch Mal Coeur 57 433 1964

12 Wada J Ikeda T Komatsu S Ikeda K Endo T and Sato T Right ventricular myxoma. Report of a case diagnosed preoperatively and removed successfully Ann Thorac Surg 1 84 1965

13 Sakakibara S Osawa M Konno S Hashimoto A Gomi H Miyamoto A M and Takao A Myxoma of the right ventricle of the heart Report of a case with successful removal and review of the literature Am Heart J 69 382 1965

14 Byron F X and Thomson W P Myxoma of the right ventricle Ann Thorac Surg 2 424 1966

15 Morrow A G Kahler R L and Reis R L Primary myxoma of the right ventricle Clinical hemodynamic and angiographic findings before and following operative treatment Am J Med 40 954 1966

16 Krause S Adler L N Reddy P S and Magovern G J Intracardiac myxoma in siblings Chest 60 404 1971

17 Warembourg H Ducloux G Pauchant M Delbecque H Carre A and Dubar P Les myxomes du ventricule droit Arch Mal Coeur 64 1557 1971

18 Simcha A Wells B G Tyana M J and Waterston D J Primary cardiac tymours in childhood, Arch Dis Child 46 508 1971

19 Hubbard T F and Neil R N Myxoma of the right ventricle Report of a case with unusual findings Am Heart J 81 548 1971

20 Zager J Smith J O Goldstein S and Franch R H Tricuspid and pulmonary valve obstruction relieved by removal of a myxoma of the right ventricle Am J Cardiol 32 101 1973

21 DeMaria A N Vismara L A Miller R R Neumann A and Mason D T Unusual echographic manifestations of right and left heart myxomas Am J Med 59 713 1975

22 Nakata K Onouchi Z Tomisawa M Goto M Go... M Furukawa N Kusunoki T Watanabe T Asa...ma S and Asayama J Right ventricular myxoma in infancy Jap Circ J 40 1183 1976

23 Dang C R and Hurley E J Contralateral recurrent myxoma of the heart Ann Thorac Surg 21 59 197...

24 Lieber G A Magovern G J Park S B Cushing W J Begg F R and Joyner C R Familial myxomas in ... siblings J Thorac Cardiovasc Surg 71 605 1976

25 Geddes D M and Kerr I H Case reports Pulmonary arterial aneurysms in association with a right ventricular myxoma Br J Radiol 49 3 4 1976

26 Snyder S N Smith D C Lau F Y K and Turner A F Diagnostic features of right ventricular myxoma Am Heart J 91 240 1976

27 Chandraratna P A N Pedro S S Elkins R C and Grantham N Echocardiographic angiographic and surgical correlations in right ventricular myxoma simulating valvar pulmonic stenosis, Circulation 55 ... 1977

28 Nanda N C Barold S S Gramiak R Ong L S and Heinle R A Echocardiographic features of right ventricular outflow tumor prolapsing into the pulmonary artery Am J Cardiol 40 ... 197...



Fig 6 Photograph of myxoma exposed by incision of the right ventricular outflow tract

A peculiar diastolic sound resembling that reported by us was described and presented in phonocardiograms of only three cases Sakakibara and associates[13] called this sound which was separated by 130 msec from A and abnormal vibratory phenomenon [13] and Chandraratna and co workers [7] suggested that the sound was a tumor plop rather than P since it was greatly delayed (140 to 160 msec) after A_2 Chandraratna and colleagues observed that the diastolic sound a low pitched thud was coincident with maximum anterior motion of the tumor and with the closure of the pulmonary valve by echophonocardiography Snyder and associates recorded a similar sound and speculated that it might be the delayed closure of the pulmonary valve (150 msec. from A) This explanation was subsequently questioned by Levisman[3] who noted that the sound in question occurred after the v wave of the accompanying jugular venous pulse tracing It should be noted that in these three cases the myxoma had prolapsed through the pulmonary valve just as in our case

Our patient had a sound of short duration in mid-diastole The onset of this vibration coincided with the most anterior position of the tumor in the right ventricular outflow tract by M mode echocardiography This relationship of the impact of the tumor on the right ventricular wall and the appearance of the sound was confirmed from frame-by frame analysis of the tumor movement as determined by angiography We feel that

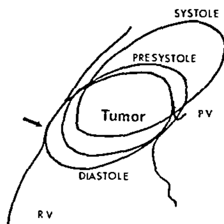


Fig 7 Diagram illustrating the movement of the tumor traced from angiographic frames In mid-diastole the tumor comes in contact with the free wall of the right ventricular outflow tract *(arrow)* With atrial and ventricular contraction the tumor is propelled forward through the pulmonary valve *(PV)* The configuration of the right ventricle *(RV)* and PV is taken from an angiographic frame in mid-diastole at the moment of impact of the tumor on the right ventricular wall

this explanation of the genesis of the sound is more reasonable than ascribing it to a much delayed P_2 The sound occurred 150 msec from A which is beyond even the longest separation of A P in the patients with pulmonary stenosis studied by Leatham and Weitzman [3]

In view of these considerations the diastolic sound in the reports of Sakakibara and associates and Snyder and colleagues probably also repre

Torsades de pointes as a manifestation of mexiletine toxicity

G Cocco M D
C Strozzi M D
D Chu Ph D
R Pansini M D
Ferrara Italy

Mexiletine a new antiarrhythmic agent, has recently been released for clinical use Structurally related to lidocaine it belongs to the class of local anesthetic antiarrhythmic agents [1, 2] Unlike lidocaine however mexiletine is active following oral administration and has a plasma half life varying between 8 and 20 hours [2] We report a case of mexiletine toxicity associated with an atypical ventricular tachycardia

Case report

A 59 year old man was sent to our Cardiological Department University of Ferrara on December 28 1979 with a diagnosis of coronary heart disease (CHD) ventricular arrhythmias and gastrointestinal intolerance to quinidine A ventriculography in May 1978 had revealed a septal hypokinesia mild cardiomegaly and a left ventricular end diastolic pressure of 23 mm Hg The left ventricle was abnormal (bulged) by palpation and a 2/6 holosystolic high pitched murmur was heard on the mitral area and at the apex The electrocardiogram (ECG) revealed a normal sinus rhythm at a heart rate (HR) of 70 beats/minute rare unifocal ventricular premature complexes (VPC s) and nonspecific ST T changes The P R interval was 0 17 sec the QRS duration 0 09 sec and the QT interval was 0 46 sec Sitting blood pressure (BP) was 125/80 mm Hg and the patient s weight was 78 5 kilograms A 24 hour dynamic ECG revealed multifocal VPC s (1 230 in 24 hr) couplets and runs and three sustained runs of ventricular tachycardia (Fig 1) Lidocaine was given intravenously at a 1 mg/kg loading dose followed by 2 5 mg/minute and it reduced the number of VPC s by over 85% Neither couplets nor runs were observed during the [illegible] hour therapy and observation period It was then decided to treat this patient with mexiletine 100 mg every 6 hr Since the patient did not present with angina pectoris with the possible exception of perhaps one slight episode during effort every 10 days we decided to treat angina only by sublingual nitroglycerin whenever necessary No other therapy was prescribed The patient was requested to come every 10 days for regular checkups Seven days later the patient came complaining of dizziness occasional palpitations and increasing dyspnea A 8-hour dynamic ECG revealed a very good control of the previous VPC s however a new and severe form of ventricular arrhythmia namely a variant of ventricular arrhythmia (Fig 2) was detected At this time the plasma electrolytes were normal potassium 4 4 mEq/L sodium 143 mEq/L calcium 4.9 mEq/L and magnesium 1 6 mEq/L The physical status was practically unchanged Mexiletine was immediately stopped and two 24 hour dynamic ECG s were obtained The ventricular tachycardia did not recur but the VPC s increased progressively and 18 hours after stopping mexiletine they reached the number and the type that were previously seen The patient was then treated with disopyramide 100 mg every 8 hr and atenolol 50 mg/day Three 24 hour and [illegible] 12 hour dynamic ECG s were obtained at 6- to 15-day intervals With this therapy the number of VPC s decreased by 65% to 76% and the couplets or runs were no longer observed Until the time of writing (February 14 1980) the patient felt relatively well and does not complain of palpitations syncopes or related symptoms Ventricular tachycardia has not been observed

Discussion

This patient s arrhythmia seen during mexiletine treatment represents a variant of ventricular tachycardia and we believe that it fulfill the criteria for the torsades de pointes We could not document the origin of this torsade de pointes by means of electrophysiological studies However we believe that it was of ventricular origin Indeed no P waves were evident The atypical rhythm resembles some of the patient s previous VPC s The patient had also had previous episodes of ventricular tachycardia though more

From the Card [illegible] g D [illegible] Med University of Ferrara Ferrara Italy

Received for publ [illegible] M [illegible]
Accepted for publ [illegible] Ap [illegible]

Reprint requests [illegible] seppe C [illegible] M D Postfach 290 CH-4103 Bottmingen Switze [illegible]

0002-8 03/80/120878 + 03500 30/0 © 1980 The C V Mosby Co

29 Ports, T A Schiller N B and Strunk B L Echocardiography of right ventricular tumors Circulation 56 439 1977
30 Roelandt J Bletter W B Leuftink E W van Dorp W G ten Cate F and Nauta J Ultrasonic demonstration of right ventricular myxoma J Clin Ultrasound 5 191 1977
31 Sasaki S Lin Y T., Redington J U Mendez A M Zubiate P and Kay J H Primary intracavitary cardiac tumore A review of 11 surgical cases J Cardiovasc. Surg 18 15 1977
32 Melendez, L J Sears G A and Coels J C Right ventricular tumour demonstrated by echocardiography Can Med Assoc J 118 62 1978
33 Sun, R. K Pattankar V L Singh H Aikat B K., and Gujral J S Myxoma of the tricuspid valve Aust N Z J Surg 48 490 1978
34 Powers J C Falkoff M Heinle R A., Nanda N C Ong L. S., Weiner R S and Barold S S Familial cardiac myxoma Emphasis on unusual clinical manifestations J Thorac Cardiovasc Surg 77 782 1979
35 Levisman J A The phonocardiogram in right ventricular myxoma (Letter to the editor) AM HEART J 92 673 1976
36 Leatham A and Weitzman D Auscultatory and phonocardiographic signs of pulmonary stenosis Br Heart J 19 303 1957

Note references 4 and 11 deal with the same case

ciated with a variety of cardiac diseases Its oral effectiveness its relatively long duration of action and the relatively low incidence of serious side effects indicate that this drug has its place among the antiarrhythmic agents However though rarely mexiletine similar to the other antiarrhythmic drugs of the local anesthetic type may cause the feared torsades de pointes Until now this side effect had not been observed with lidocaine and it was therefore surprising that mexiletine electrophysiologically and chemically similar to lidocaine could indeed induce this arrhythmia

Summary

An episode of torsades de pointes an unusual ventricular tachyarrhythmia developed in a 59 year old coronary patient who was treated with 100 mg four times a day mexiletine orally The PR QRS and QT intervals were normal The ventricular arrhythmias resembled in part the patient s previous ventricular premature complexes but there were some relevant morphological differences The plasma electrolytes were within normal limits Mexiletine which is chemically and electrophysiologically similar to lidocaine probably caused this arrhythmia Although mexiletine is a useful antiarrhythmic drug it should be added to the list of drugs associated with atypical ventricular tachycardia

The authors wish to express their gratitude to Ms C Fan for her secretarial assistance

REFERENCES

1 Chew C Y C Collet J and Singh, B N Mexiletine a review of its pharmacological properties and therapeutic efficacy in arrhythmias Drugs 17 161 1979
2 Danilo P Jr Mexiletine Am Heart J 97 399 1979
3 Kossmann C E Torsade de pointes an addition to the nosography of ventricular tachycardia Am J Cardiol 42 1054 1978
4 Jenzer H R and Hagemeijer F Quinidine syncope torsade de pointes with low quinidine plasma concentrations Europ J Cardiol 4 447 1976
5 Koster R W and Wellens H J J Quinidine-induced ventricular flutter and fibrillation without digitalis therapy Am J Cardiol 38 519 1976
6 Meltzer R S Robert E W McMorrow M and Martin R P Atypical ventricular tachycardia as a manifestation of disopyramide toxicity Am J Cardiol 42 1049 1979
7 Siklos P Chalmers T M and Evans, D W Ventricular tachycardia after disopyramide Lancet 1 98 1978
8 Tri, T B Disopyramide induced syncope Am J Cardiol 44 391 1979
9 Fazzini P F Ventricular tachycardia a new iatrogenic possibility Am Heart J 90 805 1975
10 Puritz R., Henderson, M A Baker S N and Chamberlain D A Ventricular arrhythmias caused by trimipramine Br Med. J 2 608 1977



Fig 1A Representative strip of the 24 hour dynamic ECG (bipolar chest lead) prior to mexiletine administration This strip shows an example of ventricular couplets

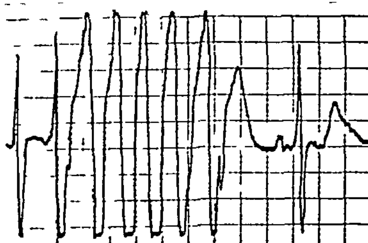


Fig 1B Representative rhythm strip a in *Fig 1A* This strip illustrates an example of runs of ventricular tachycardia



Fig 2 A representative strip of the 8-hour ECG (bipolar chest lead) showing ventricular tachycardia during mexiletine administration

logically different The PR and QRS intervals immediately before and after this episode of torsades de pointes were within normal limits and the QT did not appear to be pathologically increased Since the plasma electrolytes were within normal limits they cannot be held responsible for this arrhythmia We believe that this torsade de pointes was induced by mexiletine Quinidine [5] disopyramide [6] and also other antiarrhythmics of the local anesthetic type have been found to cause this arrhythmia However quinidine generally induces this arrhythmia in conjunction with a QT prolongation Disopyramide may also prolong the QT interval [4] The rare broadening of the QRS complex induced by mexiletine [2] was not observed in this patient Although we did not obtain plasma levels for mexiletine there were no signs of toxicity Furthermore the patient did not present any signs of renal or hepatic failure It is therefore unlikely that this side effect was secondary to an excessively high dose of mexiletine

Conclusions

Mexiletine is a useful antiarrhythmic agent effective against ventricular arrhythmias asso

ciated with a variety of cardiac diseases Its oral effectiveness its relatively long duration of action and the relatively low incidence of serious side effects indicate that this drug has its place among the antiarrhythmic agents However though rarely mexiletine similar to the other antiarrhythmic drugs of the local anesthetic type may cause the feared torsades de pointes Until now this side effect had not been observed with lidocaine and it was therefore surprising that mexiletine electrophysiologically and chemically similar to lidocaine could indeed induce this arrhythmia

Summary

An episode of torsades de pointes an unusual ventricular tachyarrhythmia developed in a 59 year old coronary patient who was treated with 100 mg four times a day mexiletine orally The PR QRS and QT intervals were normal The ventricular arrhythmias resembled in part the patient s previous ventricular premature complexes but there were some relevant morphological differences The plasma electrolytes were within normal limits Mexiletine which is chemically and electrophysiologically similar to lidocaine probably caused this arrhythmia Although mexiletine is a useful antiarrhythmic drug it should be added to the list of drugs associated with atypical ventricular tachycardia

The authors wish to express their gratitude to Ms C [illegible] for her secretarial assistance

REFERENCES

1 Chew C Y C Collet J and Singh B N Mexiletine a review of its pharmacological properties and therapeutic efficacy in arrhythmias Drugs 17 161 1979
2 Danilo P Jr Mexiletine Am Heart J 97 [illegible]
3 Kossmann C E Torsade de pointes an addition to the nosography of ventricular tachycardia Am J Cardiol 42 1054 1978
4 Jenzer H R and Hagemeijer F Quinidine syncope torsade de pointes with low quinidine plasma concentrations Europ J Cardiol 4 447 1976
5 Koster R W and Wellens H J J Quinidine-induced ventricular flutter and fibrillation without digitalis therapy Am J Cardiol 38 519 1976
6 Meltzer R S Robert E W McMorrow M and Martin R P Atypical ventricular tachycardia as a manifestation of disopyramide toxicity Am J Cardiol 42 1049 1979
7 Siklos P Chalmers T M and Evans D W Ventricular tachycardia after disopyramide Lancet 1 [illegible]
8 Tri T B Disopyramide induced syncope Am J Cardiol 44 391 1979
9 Fazzini P F Ventricular tachycardia a new iatrogenic possibility Am Heart J 90 805 19[illegible]
10 Puritz R Henderson M A Baker S N and Chamberlain D A Ventricular arrhythmias caused by prenylamine Br Med J 2 608 19[illegible]

Cardioversion and defibrillation

Regis A DeSilva M B F R C P (C)
Thomas B Graboys M D
Philip J Podrid M D
Bernard Lown M D
Boston Mass

Historical background

The use of electrical energy for reverting diverse cardiac tachyarrhythmias has in the last 20 years become standard practice because of its safety and reliability Contemporary clinical cardiology and cardiac surgery have been significantly affected by the ready availability of a simple method for terminating atrial and ventricular arrhythmias But interest in electricity for medical use is hardly contemporary Preoccupation with galvanic current both for amusement and for resuscitation can be documented in the eighteenth century [1] Possibly the earliest case of successful resuscitation was that of a three year old child who was shocked through the chest by a discharge from a Leyden jar by a Mr Squires of London [2]

The earliest recorded experimental approach to the use of electrical shock for resuscitation was that of Abildgaard[3] in 1775 He shocked hens delivering a sufficient charge to render them lifeless Subsequent shocks revived the birds and he noted that shocks to parts other than the chest were ineffective Abildgaard was unaware of ventricular fibrillation (VF) as this arrhythmia was described only in 1849 by Ludwig and Hoffa Based on extensive physiological studies of the heart McWilliam suggested in 1889 that VF was the mechanism of sudden death a conclusion which is sanctioned by contemporary observations In 1899 Prevost and Battelli [7] while investigating the effects of electricity on animals noted that weak currents induced and strong AC or DC currents terminated VF A reliable method to terminate VF had to await further developments

With the introduction of the dynamo and the development of commercially available electric power a new industrial hazard emerged The first electrocution in the USA occurred in 1879 and this number grew rapidly It soon became apparent that such deaths were due to VF Kouwenhoven and his colleagues[9-] examined both AC and DC circuits for defibrillation and concluded that AC gave superior results They also studied the effects of chest massage which had been commented on previously by Prevost and Battelli in their defibrillation studies Ferris and co workers [1] in 1936 succeeded in closed chest defibrillation in sheep using AC The culmination of these studies came in 1947 when Beck and colleagues defibrillated the exposed human heart at surgery with complete recovery of the patient Closed chest defibrillation in man was first accomplished again using an AC device in 1956 by Zoll and co workers [15]

Up until the early 1960 s AC was thought to be the definitive measure for defibrillation The earlier work of Gurvich and Yuniev[16] in the Soviet Union and of McKay and Leeds[18] in the United States established a basis for the exploration of DC or capacitor discharge Subsequent investigations by Peleska[19-21] outlined the physiologic and pathologic consequences of electrical discharge as well as the circuit characteristics for safe defibrillation Contemporaneous studies by Lown and co workers [4] demonstrated that DC

From the Cardiovascular Division, Department of Medicine Peter Bent Brigham Hospital and the Cardiovascular Laboratories, Department of Nutrition, Harvard School of Public Health, Boston Mass.
Received for publication on March 19 1979
Reprint requests Bernard Lown, M D Professor of Cardiology Department of Nutrition Harvard School of Public Health, 665 Huntington Ave Boston MA 02115

0002-8703/80/120881 + 15$01 50/0 © 1980 The C V Mosby Co

especially important to record since immediately following reversion the P waves may be diminutive in the limb leads and the rhythm may be irregular The interpretation would then be of continued atrial fibrillation if this is the rhythm being treated and the patient is thereby subjected to unnecessary discharges at higher energies

C Anticoagulation Anticoagulation prior to cardioversion is unnecessary in the patient with the acute onset of atrial fibrillation or if its duration has been less than a week However many patients who are aware that they have experienced a change in rhythm underestimate the time onset of the fibrillation Thus in view of the potential for embolic events within this group of patients we routinely anticoagulate patients for a period of three weeks prior to cardioversion Following cardioversion anticoagulation is maintained for one month Other atrial arrhythmias do not require anticoagulant drugs

Termination of specific arrhythmias

1 *Atrial fibrillation* Prior to the introduction of cardioversion restoration of sinus rhythm was time consuming and hazardous requiring the use of increasing doses of quinidine on successive days This was carried out until the patient became either very ill or until sinus rhythm was restored The procedure frequently required a week or more The initial experience by Lown and co workers [7] from this laboratory detailed results with cardioversion among 50 patients with 65 episodes of atrial fibrillation In this group of patients the arrhythmia was successfully terminated in 58 of 65 or 89% of episodes The results were particularly striking in view of the fact that many of the patients had been in chronic fibrillation over many years that these patients were largely resistant to quinidine reversion and that in a number cardioversion was carried out immediately after mitral valvular operation Energy requirements for reversion are a function of the duration of the rhythm disorder Thus patients with atrial fibrillation in excess of six months required a mean energy of 150 wsec while those with AF of less than three months required 100 wsec The size of fibrillation or 'f' waves in Lead V_1 provides an important clue as to the energy requirement and whether indeed cardioversion will succeed The energy for reversion is inversely related to the size of the 'f' wave Thus when three groups of 50 patients each were segregated as to 'f' wave amplitude those having less than 1 mm amplitude required 140 wsec in those with dimensions of 1 0 to 2 0 mm 116 wsec was effective while in those exceeding 2 0 mm 9? wsec was required [4] It is our practice to titrate energies to 400 wsec if necessary However 9? of patients are usually reverted with 200 wsec or less

When patients are electrically reverted from atrial fibrillation several outcomes are observed A fairly common sequence involves long periods of sinus node asystole with junctional escape followed rapidly by sustained sinus bradycardia with a gradually accelerating rate This has been designated as the somnolent sinus syndrome and reflects recovery of the sinus node from prolonged overdrive suppression by chaotic atrial depolarizations A less common sequence involves an ever changing sinus rate with differing P wave morphologies Bradycardia alternating with variable atrial rhythm and multiple atrial premature beats as well as paroxysms of tachycardia are additional hallmarks of this syndrome which Lown designated the "sick sinus syndrome" [4] Generally such abnormalities in generation and conduction of the sinus impulse are observed following cardioversion of patients with atrial fibrillation of several years duration It frequently augurs the prompt recurrence of atrial fibrillation Among patients with recent onset of atrial fibrillation neither of the above sequences occurs A "strong" sinus rhythm with an unchanging P wave follows within 1 0 to 3 0 seconds after the electrical shock The rate is sustained between 60 to 90 per minute without arrhythmia or interrupted by occasional atrial ectopic beats

Maintenance of sinus rhythm is facilitated by the use of antiarrhythmic drugs specifically quinidine We initiate this agent 24 to 48 hours prior to cardioversion in divided doses totalling 1 2 grams daily Use of quinidine reduces the energy for cardioversion effects a 10% to 15% pharmacologic reversion to sinus rhythm and stabilizes the atrium thereby decreasing the likelihood of post cardioversion recurrence of arrhythmia [4] The prolongation of the QT interval by quinidine is generally without hazard except in a small number of patients who have mitral valvular regurgitation and a high frequency of ventricular premature beats These patients are at a higher risk of

selected for triggering the electric discharge The physiologic basis for cardioversion is that electrical discharge depolarizes part of the reentrant pathway that is non refractory Once an arrhythmia is initiated it may be self sustaining Continuation of the arrhythmia may be due to the existence of a reentering wavefront of excitation traversing a fixed or a variable pathway The advancing wavefront of depolarization is separated from its tail by fully recovered tissue the so-called excitable gap Depolarization of the excitable tissue in the reentry circuit will essentially close the gap preventing sustenance of the arrhythmia That such depolarization of the excitable gap is indeed the basis for the effectiveness of cardioversion is supported by the observation that this technique is equally effective irrespective of where in the cycle the discharge is delivered The above explanation accords with current electrophysiologic understanding It does not explain however why arrhythmias such as fibrillation be they atrial or ventricular require larger energies than those necessary for atrial flutter or ventricular tachycardia

Method of cardioversion

The procedure should be fully explained to the patient to allay anxiety as the amount of energy required is related to the level of agitation and unease Cardioversion should be performed following an overnight fast or omitting the previous meal in more urgent cases Intubation is not necessary If the patient is on a digitalis drug this medication need not be withheld Serum levels of digoxin and electrolytes should be obtained on the day prior to the procedure Prothrombin time is obtained if the patient has been anticoagulated for atrial fibrillation Cardioversion is preferably carried out early in the day in a room equipped for cardiopulmonary resuscitation There should be a minimum of personnel and activity The patient should be warm comfortable and unencumbered by tight fitting clothes An intravenous infusion is started for drug administration Blood pressure is monitored prior to and during administration of the anesthetic Once the procedure is completed the patient is electrocardiographically monitored for one hour before being released

A Anesthesia Initial sedation is provided by administering 100 mg of phenobarbital intramuscularly an hour before the procedure The sedation thus provided reduces the amount of diazepam (Valium) to be given subsequently At the time of cardioversion an initial intravenous dose of 5 mg of diazepam is administered followed by 2 5 mg increments every two to three minutes Both blood pressure and respiratory rate are monitored prior to each dose The average amount of diazepam required to achieve adequate sedation with amnesia in over 500 cardioversions was 15 mg although the range is quite variable and up to 50 mg may be administered without ill effects

B Cardioversion technique The main danger in transthoracic electric discharge is the provocation of VF The current generation of cardioverters incorporates an automatic mode which displays and inscribes the precise location of the capacitor discharge on the R wave The lead which best displays the highest R wave amplitude should be selected for discharge synchronization The risk of provoking ventricular fibrillation in a nonsynchronized discharge is less than 5% Improper synchronization may result when the electrocardiographic signal contains artefactual spikes when there are extremely prominent T waves and in bundle branch block when the R wave is taller than the R wave

Both anteroposterior and anterolateral electrode positions have been employed in cardioversion and defibrillation The anteroposterior position reduces energy requirements by 50% and thus potential complications are reduced [2] [4] The anterior electrode is held firmly along the right sternal border at the level of the second and third intercostal spaces while the posterior electrode is placed at the angle of the left scapula The electrodes must be completely covered with conductive gel particularly along the edges to reduce the likelihood of skin burns

During elective cardioversion energy titration should be employed with an initial setting at 5 wsec Low energies may disclose rhythm disturbance in patients with subclinical digitalis toxicity or electrolyte disturbance and may also reduce myocardial damage The emergence of ventricular arrhythmia in such circumstances requires prompt use of lidocaine The procedure is then continued utilizing increasing energies of 10 25 50 100 200 300 and 400 wsec until reversion occurs After each successive discharge monitoring of Lead II or V_1 will assist in defining the resumption of sinus rhythm The latter lead is

necessity in these cases In many of these patients we deliberately attempt to induce this chronic rhythm disorder as the rhythm of choice

2 Supraventricular tachycardia The majority of supraventricular tachycardias (SVT) do not require cardioversion as they usually respond to vagal maneuvers Vassaux and Lown[5] found that patients coming to cardioversion for SVT had been hospitalized with that arrhythmia for several days and had failed to revert despite the use of a variety of antiarrhythmic agents There has been a reluctance to employ cardioversion for the patient with organic heart disease who experiences SVT In part this is due to the fact that digitalis overdose may be responsible for paroxysmal atrial tachycardia with or without block Cardioversion of such patients may be hazardous Indeed death has been reported following cardioversion in patients with digitalis induced supraventricular mechanisms[3,33] Yet the greatest urgency for reversion to normal rhythm may exist in patients with these very arrhythmias Since these arrhythmias frequently occur in patients with substantial organic heart disease and significant congestive manifestations the rapid ventricular rate encroaches further upon an already compromised ventricular reserve If the mechanism is due to digitalis intoxication cardioversion is contraindicated If however the likelihood of such intoxication is remote cardioversion is the measure of choice Titration of energy permits safe reversion of digitalized patients with SVT

Occasionally clinical circumstances do not clearly define the presence of digitalis toxicity Cardioversion may then be employed as a diagnostic modality The emergence of ventricular ectopic activity or higher degrees of atrioventricular block without reversion to sinus rhythm at low energies strongly suggest digitalis toxicity When ventricular arrhythmias are provoked these are promptly controlled with intravenous lidocaine If after successive discharges the ectopic mechanism is not abolished but ventricular ectopic beats increase in frequency multiformity and repetitive pattern it is likely that overdigitalization is the underlying condition and it is best to desist from further attempts at cardioversion

3 Atrial flutter Prior t[illegible] [illegible] [illegible]dvent of cardioversion, atrial flutter was [illegible] the most difficult arrhythmias to manage Alth[illegible]h the mechanism for this arrhythmia h[illegible] [illegible]een definitely established clinical and experimental evidence indicates that it is the result of a circus movement as defined by Lewis and associates[3] This arrhythmia is often refractory to the conventional antiarrhythmic agents including quinidine procainamide propranolol and disopyramide Large and often toxic doses of digitalis glycosides may be required in order to obtain ventricular rate control and even then difficulty in producing consistent block at the atrioventricular junction results in episodic ultra rapid rates with troublesome palpitation It may be life threatening if 1 1 A V conduction should develop Cardioversion is now the method of choice for terminating atrial flutter Numerous reports have documented that this technique is 72% to 100% effective[4,5,31,3] Lown[4] found that atrial flutter is successfully terminated in 97% of cases The effective energy is generally less than 50 wsec with the average requirement of 25 wsec in over 200 patients studied with this arrhythmia Usually only a single discharge is necessary

When atrial flutter is recurrent notwithstanding the use of antiarrhythmic drugs when the arrhythmia recurs shortly after successful cardioversion, or if cardioversion is unsuccessful in restoring normal sinus rhythm it is our practice to attempt to establish atrial fibrillation as the rhythm of choice This can be accomplished by the use of large doses of digitalis glycosides following which atrial fibrillation may emerge Another therapeutic option is to utilize a low energy discharge during cardioversion The technique is more effective and carries less morbidity Experimental and clinical data have shown that if a stimulus is applied to the vulnerable period of the atrium atrial fibrillation will occur[3] Since flutter is likely to be a reentrant mechanism some parts of the atria are always undergoing depolarization while other parts are in a state of refractoriness or incomplete repolarization Thus the vulnerability to fibrillation is present throughout the flutter cycle and a low energy discharge given at any time in the cardiac cycle stimulating some incompletely recovered atrial tissue will convert atrial flutter to fibrillation About 50% of subjects with atrial flutter who receive such low energy discharges will develop atrial fibrillation if the shock is inadequate to restore sinus rhythm The median shock necessary to induce fibrillation with this method is 1[illegible] wsec with a range of 1 to 20 wsec

experiencing quinidine syncope It may be wise to substitute another antiarrhythmic agent in these cases Maintenance of sinus rhythm beyond 12 months is accomplished in *less than one half* of patients with atrial fibrillation [47] This is particularly true for the patient whose atrial fibrillation is associated with altered left ventricular function

Determination of which patients are suitable for elective cardioversion from atrial fibrillation requires careful assessment of the patient and knowledge of contraindications of the procedure Cardioversion may not succeed or is relatively contraindicated in the following groups of patients with atrial fibrillation

(a) Atrial fibrillation of prolonged duration Higher energies are required for reversion of atrial fibrillation of prolonged duration and the success rate is low We generally limit elective cardioversion to patients who have been in chronic atrial fibrillation for less than one year In those with arrhythmia of longer duration sinus rhythm *is unlikely* to persist in more than *half* the patients [4, 7, 51]

(b) Mitral valvular disease with markedly enlarged left atrium Chronic mitral regurgitation or stenosis alters both the size and mean pressure of the left atrium This provides conditions for a sustained fractionation of reentrant excitability and is particularly the case in those having a giant left atrium secondary to mitral regurgitation Prior to the onset of atrial fibrillation a number of these patients will have exhibited first degree atrioventricular block and frequent atrial premature beats, which are associated with relapse of atrial fibrillation While reversion to sinus rhythm is simple maintenance of a normal mechanism with current antiarrhythmic drugs is often difficult or even impossible

(c) Atrial fibrillation in the setting of left ventricular failure The patient experiencing altered left ventricular *function may* develop acute atrial fibrillation secondary to elevated left sided filling pressures and subsequent atrial distension This may be the clinical setting of a patient with an acute myocardial infarction In this situation the use of digitalis drugs to decrease the ventricular response to atrial fibrillation thus improving ventricular function will usually result in restoration of sinus rhythm Myocardial infarction is however not a contraindication for electrical reversion Cardioversion carried out in the patient with severe pulmonary congestion will probably not restore sinus rhythm especially when atrial fibrillation was not the initiating factor Occasionally a patient with a far advanced cardiomyopathy who is anticoagulated will benefit from the augmentation of cardiac output derived from even a brief period of sinus rhythm Hence the management of this type of patient might include periodic cardioversion

(d) Lone atrial fibrillation Atrial fibrillation is not uncommon in the absence of demonstrable heart disease The left atrial and left ventricular chambers are usually normal in size and fibrillatory waves are diminutive in Lead V_1 Maintenance of sinus rhythm is difficult despite the use of antiarrhythmic agents and cardioversion is of limited application However there exist no prior methods for ascertaining the patient who will sustain sinus rhythm for either long periods or even permanently It is therefore worthwhile to subject such patients to at least one cardioversion

(e) Atrial fibrillation with a slow ventricular response The majority of patients with acute atrial fibrillation exhibit a ventricular response in excess of 130 beats/minute Frequently one encounters an elderly patient not receiving digitalis or beta adrenergic blocking agents whose ventricular response is 70 beats/minute or less The absence of tachycardia most probably reflects the coexistence of atrioventricular conduction disturbance Reversion to sinus rhythm may be associated with extreme bradycardia requiring the use of a permanent pacemaker Atrial fibrillation is far preferable in these cases

(f) Adverse reaction to antiarrhythmic agents Maintenance of sinus rhythm following cardioversion requires the use of chronic antiarrhythmic therapy Thus patients who are unable to tolerate antiarrhythmic drugs such as quinidine or disopyramide or who experience a recurrence of arrhythmia on these drugs may not be candidates for cardioversion

(g) Recurrent atrial tachyarrhythmias Patients with chaotic arrhythmias (Parkinson Papp syndrome) or those with oft recurring atrial tachyarrhythmias flourish once atrial fibrillation becomes established They no longer are disabled by the frequent paroxysms with the onset of atrial fibrillation Thus atrial fibrillation is the preferred rhythm and becomes a therapeutic

chest massage and correction of acid base balance delivery of two or three 400 wsec shocks in rapid sequence as a last resort may be successful

Reversion during pregnancy Pregnancy may be the setting for recurrent atrial arrhythmias which may be resistant to pharmacologic therapy and cardioversion[7] However both elective and emergency reversion have been performed with safety during all three stages of pregnancy[72,77] Schroeder and Harrison[76] reported seven episodes of cardioversion for PAT in one patient during various stages of pregnancy In all attempts 100 wsec terminated the abnormal rhythm Grand and Bernard[77] used 300 wsec to revert atrial fibrillation successfully without disruption of fetal heart rhythm However suspected fetal distress necessitated cesarean section for delivery In other reports[73,75] cardioversion did not induce premature labor Defibrillation during pregnancy presents no real therapeutic dilemma as death of the mother and the fetus will almost certainly supervene otherwise Curry and Quintana[8] reported the successful termination of VF during acute myocardial infarction with a single 300 wsec shock The fetal ECG was unaffected by the discharge but the mother was subsequently found dead presumably as a result of recurrent VF

Fetal rhythm should be monitored during cardioversion Induction of VF by the electrical discharge during the fetal ventricular vulnerable period is remote and the energy reaching the fetal heart is minuscule Furthermore it is known that the hearts of small mammals can be fibrillated only with great difficulty and the disordered rhythm is often self terminating This is presumably because a critical myocardial mass is necessary to sustain VF

Complications

a Morphologic and functional damage A large number of studies demonstrate that electrical discharge causes both morphologic and functional derangements Grossly recognizable as well as microscopic damage may occur[2 3 4 8 8] Lown and colleagues demonstrated progressive changes consistent with the release of tissue potassium as successive high energy shocks were delivered Electrically induced tissue damage is considerably less with DC as compared to AC shocks[23 24 82] Dahl and co workers[83] quantified myocardial damage by precordial mapping and by gross and microscopic pathologic studies in dogs Myocardial damage was greatest when small electrodes were used and when shocks were closely spaced They recommended that during elective cardioversion shocks be spaced at intervals of more than 3 minutes to spare the heart from damage Davis and co workers found that if energy levels less than twice the threshold strength necessary for defibrillation were delivered minimal myocardial damage occurred in dogs Progressively more severe necrosis occurred with increase in delivered energy In a similar study Van Vleet and colleagues[5] concluded that a relatively broad safety margin existed between the threshold energy required for defibrillation and the energy levels which produced significant cardiac damage and death in healthy dogs Warner and co workers found areas of permanent cardiac damage as evidenced by scarring and calcification following repeated shocks lesions were characteristically subepicardial

Following electrical shock there is release of myocardial creatine phosphokinase (MB CPK) as well as other enzymes In man myocardial damage has been examined during elective cardioversion[84] None of 27 patients who received less than 425 wsec either in single or cumulative shocks demonstrated a rise in MB CPK In two of three patients who received a cumulative delivered energy dose of more than 425 wsec MB CPK was elevated Myocardial scintigraphic studies likewise confirm that the extent of damage in dogs subjected to shocks was proportional to the quantity of energy delivered to the heart[8] It is clear from the numerous studies cited that myocardial damage certainly occurs especially with repeated high energy shocks The use of high energies with inadequate skin preparation also leads to painful skin burns Impeccable technique with proper electrode positions and adequate conductive paste should therefore be used at all times

In addition to morphologic damage functional derangements result from electric shocks Fi... kin[81] noted intracardiac temperatures as high as 47° C after shocks to the exposed heart Depression in left ventricular function and contractility may result[4 81] Koning and colleagues[1] showed in isolated perfused hearts decreases in dp dt and an increase in diastolic stiffness and left ventricular diastolic pressure following electric shocks

4 Ventricular tachycardia Ventricular tachycardia (VT) may be due to an ectopic focus or to a reentrant mechanism Enchanced automaticity is the basis for ventricular tachycardia resulting from digitalis intoxication or during the initial period following acute myocardial infarction However the most frequent mechanism is reentry This suggests that cardioversion may be useful for terminating a majority of these episodes Since the first reported case of ventricular tachycardia reverted with AC shock electrical discharge has become the standard and routinely employed therapeutic measure Cardioversion should be used expeditiously in the critically ill patient with ventricular tachycardia associated with hypotension pulmonary edema or an acute myocardial infarction when intravenous lidocaine has failed The reported success rate varies from 95% to 100% [3, 5, 59] The energy requirements are almost always less than 100 wsec As little as 1 wsec will convert some cases of ventricular tachycardia and in 80% of cases 10 wsec or less has proved adequate [6]

When ventricular tachycardia is rapid and the QRS complex is wide and bizarre in configuration a broad prominent T wave may not be distinguished from the QRS complex The disorder has been termed ventricular flutter of VT of the vulnerable period (VT) Cardioversion affords a 50% chance that the discharge will occur at the apex of the T wave instead of during inscription of the R wave In fact instead of avoiding the vulnerable period the shock is synchronized to fall precisely during its midst When confronting such a problem it is advisable to switch to the defibrillator mode and deliver a nonsynchronized shock of 100 wsec this practice diminishes the likelihood of provoking ventricular fibrillation

5 Ventricular fibrillation The vast majority of cardiac arrests are due to VF [41] Defibrillation constitutes definitive treatment for this condition and success is assured only if prompt defibrillation is accomplished Although the ideal electrode positions are not known in man it is reasonable to assume that they will approximate those for elective cardioversion of atrial and ventricular arrhythmias

Initial defibrillation in adults should be conducted with a setting between 300 to 400 wsec Lower energy settings with rapid sequential discharge as practiced by some workers [2] should preferably be employed only if the resuscitation team is highly experienced Valuable time may otherwise be lost due to inefficient or improper application of the procedure Some newer defibrillators may have energy settings in excess of 400 wsec Such devices should be used with care as the possibility of serious cardiac damage and complications is increased The initial setting should never exceed 400 wsec At present there is no evidence that energies in excess of 400 wsec are ever needed in man for defibrillation If higher energies are used prolonged periods of asystole or complete heart block may ensue resulting in resumption of VF Repeated shocks with high energy result in resumption of VF due to progressive myocardial deterioration ultimately rendering termination of VF impossible

Clearly the above recommendations are excessive for pediatric subjects Gutgesell and colleagues in studying 27 children weighing between 2 1 to 50 kilograms terminated 63 of 71 episodes of VF with shocks up to 300 wsec A setting of 2 wsec/Kg ± 10 wsec was used for most of the episodes and 91% of shocks in this range were successful in terminating VF Five of the eight failures in this series of patients occurred with the recommended energy level two occurred at lower settings and one at a higher setting The authors caution that refibrillation is not an indication to increase the energy dose At the present time there are inadequate data to make definitive recommendations for pediatric defibrillation However experience to date indicates that repeated high energy shocks are inappropriate especially for small children Defibrillation of the heart during open chest surgery is another setting where low energy shocks are used In most situations shocks of 5 to 10 wsec are adequate

Ventricular fibrillation of prolonged duration may be resistant to electric shock regardless of the amount of energy used In this situation repeated high energy shocks produce momentary asystole with resumption of fine-grain VF Such a situation requires correction of acid base imbalance and hypoxia before further attempts are made Administration of a beta adrenergic agonist such as epinephrine or isoproterenol may convert a fine-grain pattern to coarse grain VF The latter variety of VF is more susceptible to electrical termination If repeated single shocks fail to terminate VF despite adequate ventilation

following cardioversion had mitral or aortic valvular disease or left ventricular dysfunction Increase in cardiac output with return of atrial systole following cardioversion[106, 108] and concomitant depression in left ventricular function by electric shocks may be contributing factors to the development of heart failure Occasionally return of left atrial systole is delayed after cardioversion so that the disparity in outputs of the right and left sides of the heart may be expected[91, 10, 111] This may lead to an increased volume load on the left ventricle resulting in pulmonary edema

e Embolism Approximately 30% of patients with atrial fibrillation may experience spontaneous serious embolic episodes during their life time[11] The risk of embolism is increased immediately following both pharmacologic or electrical reversion to sinus rhythm In 400 patients reverted with quinidine Goldman[113] encountered an incidence of 1 5% Pulmonary as well as systemic embolization may also follow cardioversion[4, 1, 9, 111, 11] The majority of patients experiencing this complication were not receiving anticoagulants prior to cardioversion The incidence of embolism in 450 episodes of atrial fibrillation treated with cardioversion was approximately the same as following reversion with quinidine at 1 2%[4] None of 100 patients on anticoagulants experienced embolism as a complication Postponed resumption of atrial systole may account for the delayed embolism occurring several days to a week after cardioversion Ikram, Nixon and Arcan[1,9] demonstrated delayed return of left atrial activity for 3 to 6 days and in one case no atrial activity was detected for 6 weeks following cardioversion Absence of mechanical activity in left right or both atria has been commented on by other workers as well[94, 11, 111] Thus anticoagulation should be performed not only 3 weeks before but also for at least 1 week following cardioversion

f Miscellaneous complications Resnekov and McDonald noted hypotension following cardioversion in 3? of 220 patients Decrease in blood pressure is usually transient but may last several hours and generally requires no treatment Transient cardiac enzyme elevation and ST segment and T wave changes not necessarily related to significant myocardial damage may also occur[4, 93, 9] There is little information on the effects of electric shock in producing failure of implanted artificial pacemakers[11, 111] However this complication has been rarely encountered and therefore should not impede cardioversion

Damage to adjoining as well as remote structures has been reported as a consequence of the electrical discharge Pericarditis[1] ocular damage,[11] transient left recurrent laryngeal nerve paralysis[120] and vertebral fracture[1] have been described Some of these complications are due to the physical trauma resulting from body movement following high electrical energy discharge

Controversies in defibrillation

a Energy dose for defibrillation Tacker Geddes and their co workers[12, 125] have indicated that conventional devices storing 300 to 400 wsec are inadequate to defibrillate adults weighing over 70 kilograms Geddes and associates found that in animals the threshold energy for defibrillation increased with body weight Tacker and colleagues[1] reported on a series of 111 patients in whom defibrillation success ostensibly declined with increase in body weight They derived a dose response curve based on 13 subjects and concluded that a third of patients weighing over 70 kilograms could not be defibrillated They recommended a dose of 3 5 to 6 wsec/kg for successful defibrillation This opinion is not persuasive and the evidence countering it has been presented elsewhere[1, 6] The data of Tacker and associates[1, 3] and of Collins and colleagues,[1] the latter being merely an expansion of the former study were collected retrospectively and provided no information on electrode position, duration of fibrillation underlying heart disease or estimates of delivered energy Furthermore statistical analysis of the data they provide does not support their claim that heavier patients were more difficult to defibrillate In contrast to these data Kerber and Sarnat[1] showed in their detailed retrospective study that defibrillation success bore no relation to body weight On the contrary their data suggested that use of high energies was associated with decreased survival

Numerous studies show that heavy patients can indeed be defibrillated using conventional devices storing 400 wsec Several case reports[78, 12, 11] attest to the successful reversion of VF in heavy patients Prospective studies on VF by Pantridge and co workers[4] and by Crampton and associates[4] and using devices sto…

Release of potassium CPK acetylcholine and catecholamines following shocks may also occur[1] Regan and associates[9] found high levels of potassium in coronary sinus blood following transthoracic shocks to the digitalized heart The quantity of potassium released was proportional to the electrical energy delivered to the heart and they concluded that potassium release by electric shock was enhanced in the presence of digitalis glycosides

b **Cardiac arrhythmias** Peleska showed that the energy content of the shock was related to both the extent of morphologic damage as well as the severity of ventricular arrhythmia Lown and co workers[70] noted in dogs that 3% exhibited ventricular tachycardia after a single 100 wsec shock while 25% showed this arrhythmia after 200 wsec and 65% after 400 wsec Subsequent studies confirmed that ventricular arrhythmias could be evoked following defibrillation or cardioversion[51 54] In man a variety of arrhythmias have been described ranging from ventricular premature beats, bigeminy salvos of mul focal beats ventricular tachycardia and brillation These arrhythmias need not be a onsequence of myocardial damage alone When F occurs during cardioversion it is usually due) improper synchronization However a number f reports document the emergence of VF some mes leading to death several minutes or even ours after the shock[5 7] These patients had een receiving quinidine digitalis glycosides or oth at the time of onset of VF and these drugs ave been implicated in provoking this arrhyth nia[55 97]

Digitalis intoxication in particular greatly ensitizes the heart to electrical dis harge[2 30 31 56 89] In dogs an eight thousandfold ncrease in sensitivity to electric shock occurred ollowing administration of a toxic dose of ouabain as judged by the emergence of repetitive ventricular activity[30] It required 60% to 80% of the toxic dose of ouabain to demonstrate such sensitization In man Kleiger and Lown[7] found that 18 of 100 digitalized patients undergoing cardioversion showed frequent ventricular pre mature beats bigeminy or ventricular tachycardia In comparing these 18 patients with the remaining 82 the pre cardioversion electrocardiograms of the former group showed more frequently arrhythmias suggestive of digitalis toxicity These arrhythmias included ventricular premature beats junctional rhythm with or without atrioventricular dissociation and first degree heart block Two patients also had episodes of atrial tachycardia with block Patients in atrial fibrillation with ventricular rates of less than 70 per minute and episodic regularization of rhythm had an almost 50% risk of developing ventricular arrhythmias following cardioversion The grade of arrhythmia increased as a function of the discharged energy

The patients who developed VF and died as reported by Rabbino and colleagues[33] and by Ross[4] had also received high doses of electrical energy in the presence of digitalis toxicity This experience underscores the extremely hazardous nature of high discharge energies in overdigitalized patients The mechanism whereby digitalis sensitizes the myocardium to electrical shock is not clear Lown Black and Moore[100] hypothesized that electrical shock alters cation transport across cell membranes promoting efflux of cellular potassium Such losses are enhanced in the excessively digitalized heart thus promoting the emergence of life threatening ventricular arrhythmia The studies by Regan and colleagues on dogs digitalized with acetyl strophanthidin and shocked electrically provide experimental support for this hypothesis Although quinidine facilitates reversion in atrial fibrillation pretreatment with quinidine prior to cardioversion clinically has not been shown definitively to be protective against the development of subsequent ventricular arrhythmias

Electrical discharge can induce relatively more benign arrhythmias such as atrial ectopic beats and impaired atrioventricular conduction Complete heart block following cardioversion or defibrillation may also occur and its duration is a function of the amount of energy delivered Use of energies of the order of 300 to 400 wsec however may result in prolonged periods of heart block or asystole which favor the reemergence of ventricular arrhythmias including fibrillation

d **Pulmonary edema** Resnekov and McDonald[1] reported on the occurrence of pulmonary edema in four patients within 24 hours of cardioversion Subsequent studies have confirmed this finding[95 6 103 105] Among 750 patients we have seen three patients with pulmonary edema and these had pulmonary embolism It is uncertain if additional mechanisms are involved The majority of patients reported with pulmonary edema

Subsequently a single catheter system with two sets of electrodes on the same catheter has been developed The sensing unit consists of either a pressure transducer or a contraction sensor element as an integral part of the catheter The capacitor charges itself if there is absence of detectable pressure or right ventricular contraction and discharge occurs after a preset interval if either of these two conditions persists Preliminary studies show that the method is effective in defibrillating both animal and human hearts using energies from 4 to 35 wsec

Intriguing though the concept is Lown and Axelrod[11] have questioned the merit of implanted defibrillators They point out that malfunction may result if the sensing element should become encased in fibrotic tissue or if the catheter migrates into the pericardial sac Unnecessary and possibly lethal shocks may then be delivered Even if these problems are overcome the question of periodic evaluation for adequacy of performance remains Unlike pacemakers which can easily be functionally assessed implanted defibrillators cannot be so evaluated Verification of adequacy would include not only ascertaining activation of the device exclusively by VF but delivery of a charge sufficient to defibrillate the heart For the present more conventional approaches to the problem of sudden death from VF are preferable

Summary

The use of electrical energy for the immediate treatment of atrial and ventricular arrhythmias is practical and easily applied The method though simple is the most effective method for terminating cardiac arrhythmias and is associated with only a low risk if properly employed In symptomatic patients the utilization of cardioversion reduces patient discomfort and complications which may occur while awaiting pharmacologic reversion of arrhythmia At present transthoracic defibrillation is the only practical method for terminating VF Despite the safety of electrical reversion proper precautions are necessary to prevent complications In particular the discharge of excessive energies especially in the presence of digitalis toxicity promises grave and life threatening consequences The use of antiarrhythmic medications is not supplanted by cardioversion and defibrillation Rather ongoing drug therapy is frequently necessary to prevent recurrence of arrhythmia

REFERENCES

1 Dibner B Early electrical machines, Norwalk, Connecticut 1957 Burndy Library p 29

2 Annual Reports of the Royal Humane Society for the Recovery of the Apparently Drowned (London) 1, 1774

3 Abildgaard P C Tentamina electrica in animalibus instituta Societas Medical Havniensis Collectanea 2 157 1775

4 Driscol T E Ratnoff O R and Nygaard O F The remarkable Dr Abildgaard and countershock Ann Intern Med 83 8 8 19

5 Wiggers C J The mechanism and nature of ventricular fibrillation Am Heart J 20 399 1940

6 McWilliam J A Cardiac failure and sudden death Br Med J 1 6 1889

7 Prevost J L and Battelli F La mort par les courants electriques—courants alternatifs a haute tension J Physiol Pathgen 1 427 1899

8 Prevost J L and Battelli F Sur quelques effets des decharges electriques sur le coeur des mammiferes Compt Rend Seances Acad Sci 129 126 1899

9 Hooker D R Kouwenhoven W B and Langworthy O R The effect of alternating current on the heart Am J Physiol 103 444 1933

10 Kouwenhoven W B The effects of electricity on the human body Bull Johns Hopkins Hosp 115 [illegible]

11 Kouwenhoven W B Jude J R and Knickerbocker G G Closed chest massage JAMA 10 [illegible]

12 Kouwenhoven W B The development of the defibrillator Ann Intern Med 71 449 1969

13 Ferris L P King B H and Spence P W Effect of electric shock on the heart Electrical Engineering (NY) 55 498 1936

14 Beck C S Pritchard W H and Feil S A Ventricular fibrillation of long duration abolished by electric shock JAMA 135 985 1947

15 Zoll P M Linenthal A J Gibson W Paul M H and Norman L R Termination of ventricular fibrillation in man by externally applied countershock N Engl J Med 254 727 1956

16 Gurvich N L and Yuniev G S Restoration of [illegible] rhythm in the mammalian fibrillating heart. Am Rev Soviet Med 3 236 1946

17 Gurvich N L and Yuniev G S Restoration of heart rhythm during fibrillation by a condenser discharge Am Rev Soviet Med 4 [illegible] 194[illegible]

18 McKay R S and Leeds S E Physiological effects of condenser discharges J Appl Physiol 6 6 195[illegible]

19 Peleska B Transthoracic and direct defibrillation Rozhl Chir 36 31 1957

20 Peleska B Cardiac arrhythmias following discharge and their dependence upon strength of and phase of cardiac cycle Circ Res 13 21 1963

21 Peleska B Optimal parameters of electrical for defibrillation by condenser discharges Circ 18 10 1966

22 Lown B Amarasingham R and Neuman J method for terminating cardiac arrhythmias—[illegible] synchronized capacitor discharge JAMA 182 1962

23 Lown B Neuman J Amarasingham R and Berkovits B V Comparison of alternating current with

400 wsec or less reverted over 95% of patients with VF These workers used either single or multiple or low energy shocks and the mean energy required for defibrillation was frequently 50% less than that recommended by Tacker and colleagues[1,1] When shocks of 200 or 300 wsec failed 400 wsec almost invariably succeeded Crampton and his group[6] found that a mean energy of 194 wsec terminated 45 of 46 episodes of VF in 11 of 12 heavy patients The patients weighed between 91 and 225 kilograms and the mean energy requirement was 1 8 wsec/kg Conventional devices storing 400 wsec thus appear to be adequate for clinical use Delivery of higher energies while likely to induce injury has yet to be shown to be necessary[1,6,130,3]

b Blind defibrillation Grace and co workers[1] have suggested that when encountering cardiac arrest immediate discharge of 200 to 400 wsec be performed in the absence of electrocardiographic confirmation of VF They argue that since VF is implicated in the vast majority of patients having an arrest prompt defibrillation provides the greatest chance for full recovery Although a controlled study was not performed they noted an increase in survival rates from 27% to 45% after blind defibrillation was started in their institution

If cardiac arrest has been presumed to exist by virtue of loss of consciousness and absence of a pulse the mechanism may be VF asystole or electromechanical dissociation The majority of patients however have been found to be in VF Prompt defibrillation will constitute definitive therapy with a minimum of delay A possible hazard exists in a very small minority of patients that they may be shocked during the ventricular vulnerable period while in rhythms other than VF If the mechanism is ventricular tachycardia use of high energies (300 to 400 wsec) will terminate the disorder rather than provoke VF This is due to the fact that a high energy discharge uniformly depolarizes the entire myocardium even if discharged during the vulnerable period Blind defibrillation with such energies is thus an acceptable risk. Electromechanical dissociation during a cardiac arrest usually signifies an unfavorable outcome In such an event it is unlikely that blind defibrillation will exert a deleterious effect on survival The uncertainty regarding the underlying rhythm disorder is resolved if the defibrillator electrodes also function as electrocardiographic monitoring leads providing confirmation of the rhythm immediately before discharge

c Chest thump Pennington Taylor and Lown[..] recommended thumpversion for malignant ventricular tachycardia They found that a precordial blow reverted 12 episodes of ventricular tachycardia in five patients in three of whom myocardial infarction was the basis for the arrhythmia The electrophysiologic basis for thumpversion is unknown However certain observations made during cardioversion suggest an explanation[5] The prefibrillatory arrhythmia designated ventricular tachycardia of the vulnerable period i e VT can be terminated with less than 1 wsec[4] Energies less than 10 wsec will terminate over 90% of episodes of VT[3] Since the small amount of energy delivered by a precordial blow is frequently sufficient to depolarize enough myocardium and initiate a propagated response by electromechanical transduction during cardiac arrest due to asystole[134] it is likely that during VT depolarization by such a blow may be adequate to interrupt a reentrant pathway and thus terminate VT Undue delay however may result in degeneration of VT to VF The steep rise in energy requirement for termination of VF then renders chest thumping ineffective

An objection to this method of reversion has been raised namely that a thump delivered during the ventricular vulnerable period may result in VF The possibility of this event occurring is less than 5% In the hospital the ready availability of a defibrillator should enable electrical termination of VF If the patient has lost consciousness cardiopulmonary resuscitation will be initiated in any case so that an immediate chest thump may be beneficial if the underlying arrhythmia is asystole or VT However the present recommendation of the American Heart Association is that chest thump be reserved for monitored patients only

d Implanted defibrillators In recent years a number of workers have demonstrated that defibrillation through an intracardiac catheter system is feasible[..] The system consists of an intracavitary right ventricular catheter containing one electrode at its tip and another in the superior vena cava alternatively a precordial subcutaneous plate may serve as the other electrode

66. Cherwek, M L., Crampton R S., and Hunter F P Human ventricular defibrillation by low energy and sequential transthoracic direct current shock, Clin Res. 25 (1) 2A 1977
67 Gascho J A., Crampton R. S., Sipes, J N., Cherwek, M L., Hunter F P., and O'Brien W M. Energy levels and patient weight in ventricular defibrillation, J.A.M.A. (In press.)
68 Gascho J A., Crampton, R. S., Cherwek, M L., Sipes J N., Hunter F P., and O'Brien, W M Determinants of ventricular defibrillation in adults, Circulation 60 231 1979
69 Gutgesell, H P., Tacker W A., Geddes L A., Davis, J S., Lie J T and McNamara D G Energy dose for ventricular defibrillation of children Pediatrics 58 898 19 6
70. Tacker W A., Rubio P A. and Reyes, L. H Low energy electrical defibrillation of human hearts during cardiac surgery J Thorac Cardiovasc. Surg 68 603 1974
71 Wagner G S and McIntosh H D The use of drugs in achieving successful DC cardioversion Progr Cardiovasc Dis. 11 431 1969
72 Robards, G J., and Saunders, P M Refractory supraventricular tachycardia complicating pregnancy Med. J Aust 2 278 1973.
73 Vogel J H K., Pryor R., and Blount S G Direct current defibrillation during pregnancy J.A.M.A. 193 970 1965
74 Meitus, M L. Fetal electrocardiography and cardioversion with direct current countershock, Dis. Chest 48 324 1965
75 Sussman, H I Duque D., and Lesser M E. Atrial flutter with 1 1 conduction Report of a case in a pregnant woman successfully treated with DC countershock. Dis Chest 49 99 1966.
76 Schroeder J S and Harrison D C Repeated cardioversion during pregnancy Am J Cardiol. 27 445 1971
77 Grand A and Bernard J Cardioversion et grossesse Nouv Presse Med 2 2327 1973.
78 Curry J J and Quintana, F Myocardial infarction with ventricular fibrillation during pregnancy treated by direct current defibrillation with fetal survival Chest 58 82 1970
79 Garrey W E The nature of fibrillary contraction of the heart Its relation to tissue mass and form Am J Physiol. 33 397 1914
80 Tedeschi, C G and White C W Jr Morphologic study of canine hearts subjected to defibrillation, electrical defibrillation and manual compression Circulation 9 916 1954
81 Rivkin L M The defibrillator and cardiac burns. J Thorac Cardiovasc Surg 46 755 1963.
82 Smith G T Beeuwkes R Tomkiewicz, M., Abe T., and Lown. B Pathological changes in skin and skeletal muscle following alternating current and capacitor discharge Am J Pathol 47 1 1965
83. Dahl, C F Ewy G A Warner E D., and Thomas E D Myocardial necrosis from direct current discharge Effect of paddle electrode size and time interval between discharges Circulation 50 ... 1974
84 Davis, J S Lie J T Bentinck D C Titus, J L., Tacker W A and Geddes L A Cardiac damage due to electrical current and energy ... Proceedings of the Cardiac Defibrillation Conf ... Purdue University West Lafayette Ind ...
85 Van Vleet J F ... ... P E Geddes, L. A., Ferrans, V ... Bright R M and Greene J A. E ... survival and acute cardiac damage induced by open-chest defibrillation of dogs, Med. Instrum. 12 55, 1978.
86 Ehsani, A., Ewy G A., and Sobel, B E. Effects of electrical countershock on serum creatine phosphokinase (CPK) isoenzyme activity Am J Cardiol 37 12, 1976
87 DiCola V C., Freedman G S., Downs S E, and Zaret B L Myocardial uptake of Technetium-99m stannous pyrophosphate following direct current transthoracic countershock Circulation 54 980, 1976
88 Warner E D Dahl C., and Ewy G A. Myocardial injury from transthoracic defibrillation countershock Arch. Pathol 99 55 1975
89 Mann F B Aberdeen E and Gerbode F L A Comparison of ventricular function subsequent to multiple defibrillations utilizing the alternating current and direct current defibrillators, Surg Forum 14 ... 1963
90 Yarbrough, R., Ussery G and Whitley J A comparison of the effects of AC and DC countershocks on ventricular function in thoracotomized dogs Am. J Cardiol. 14 ... 1964
91 Koning G Veefkind A. H and Dreschler W A Biochemical and functional characterization of cardiac damage after experimental direct defibrillation ... Med Instrum 12 55 1978
92. Childers, R. W., Rothbaum, D and Angevine J Effect of direct countershock on the electrical properties of the heart Circulation 36(Suppl II) II-85, 1967
93 Cobb F R Wallace A. G and Warner G S Cardiac inotropic and coronary vascular responses to countershock. Evidence of excitation of intracardiac nerves Circ Res 23 731 1968
94 Regan T J., Markov A., Oldewurtel, H. A and Harman M A. Myocardial K loss after countershock and the relation to ventricular arrhythmias after nontoxic doses of acetyl strophanthidin Am. Heart J 77 367 1969
95 Resnekov L. and McDonald L. Complications in ... patients with cardiac dysrhythmias treated by phased direct current shock and indications for electroversion Br Heart J 29 926 1967
96. Aberg H., and Cullhed I Direct current countershock complications, Acta Med Scand 183 415 1968
97 Gilbert R., and Cuddy R. P Digitalis intoxication following cardioversion to sinus rhythm Circulation 32 58 1965
98 Donoso E., Cohn, L. J and Friedberg C. K Ventricular arrhythmias after precordial electric shock. Am Heart J 73 595 1967
99 Sekely P Wynne N A., Pearson, D T Batson, G A. and Siderıs, D A. Direct current shock and digitalis Br Heart J 31 91 1969
100 Lown B., Black H and Moore F Digitalis, electrolytes and the surgical patient Am. J Cardiol 5 ... 1960
101 Hillestad. L., Dale J., and Storstein O Quinidine before direct current countershock A controlled study Br Heart J 34 139 1972
102 Resnekov L., and McDonald, L. Pulmonary edema following treatment of arrhythmias by direct current countershock, Lancet 1 506, 1965
103 Sutton, R B and Tsagaris, T G Pulmonary edema following direct current cardioversion Chest 57 ... 1970
104 Budow J Natarajan P and Kroop I G Pulmonary edema following direct current cardioversion for ... arrhythmia J.A.M.A 218 1803, 1971
105 Lindsey J Jr Pulmonary edema following ... sion Am Heart J 74 434 1967
106 Morris J J Entman M North W C ...

current electro hock across the chest Am J Cardiol 10 7-3, 1962

24 Lown B Electrical reversion of cardiac arrhythmias, Br Heart J 29 469 1967

25 Alexander S Kleiger R and Lown B Use of external electric counter shock in the treatment of ventricular tachycardia JAMA 177 916 1961

Lown B Bey S K Perlroth M G and Abe T Comparative studies of ventricular fibrillation J Clin Invest 42 953 1963

Lown B Perlroth M G Bey S K and Abe T Cardioversion of atrial fibrillation A report on the treatment of 65 episodes in 50 patients N Engl J Med 269 325 1963

Lown B Kleiger R and Wolff G The technique of cardioversion Am Heart J 67 282 1964

Lown B Cardioversion of arrhythmias (II) Mod Concepts Cardiovasc Dis 33 869 1964

Lown B Kleiger R and Williams B J Cardioversion and digitalis drugs changed threshold to electric hock in digitalized animals Circ Res 17 519 1965

Kleiger R and Lown B Cardioversion and digitalis II Clinical Studies Circulation 33 8 8 1966

Lown B Bey S K Perlroth M G and Abe T Cardioversion of ectopic tachyarrhythmias, Am J Med. Sci 246 257 1963

Guiney T E and Lown B Electrical conversion of atrial flutter to atrial fibrillation Flutter mechanism in man Br Heart J 34 1215 19 2

Wiggers C J The physiologic basis for cardiac resuscitation from ventricular fibrillation—method of serial defibrillation Am Heart J 20 413 1940

Schuder J C Stoeckle H Gold J H West J A and Keskar P Y Experimental ventricular defibrillation with an automatic and completely implanted system Trans. Am Soc Artif Intern Organs 16 207 19 0

Schuder J C Stoeckle H West J A Keskar P Y Gold J H and Denniston R H Experimental ventricular fibrillation in the dog with a bielectrode intravascular catheter Arch. Intern Med 132 286 19 3

Schuder J C Stoeckle H West J A and Keskar P Y Relationship between electrode geometry and effectiveness of ventricular defibrillation in the dog with catheter having one electrode in right ventricle and other electrode in superior vena cava or external jugular vein or both, Cardiovasc Res 7 6 9 19 3

Mirowski M Mower M M Staewen W S Denniston R H and Mendeloff A I The development of the transvenous automatic defibrillator Arch. Intern Med 129 7 3 19 2

Mirowski, M Mower M M Gott V L and Brawley R K Feasibility and effectiveness of low energy catheter defibrillation in man Circulation 47 79 1973

Mower M Mirowski, M Spear J F and Moore E N Patterns of ventricular activity during catheter defibrillation Circulation 49 858 1974

Zipes D P Fischer J King R M Nicoll, A de B and Jolly W W Termination of ventricular fibrillation in dogs by depolarizing a critical amount of myocardium Am. J Cardiol 36 37 1975

Ewy G A Thomas E and Taren D Electrode system for permanent implantable defibrillators transvenous catheter and subcutaneous plate electrodes Med Instrum 12 296, 19 8

3. DeBoer S Die Physiologie und Pharmakologoe des Flimmerns, Ergebn Physiol 21 1 1923

King B G The effect of electric shock on heart action with special reference to varying susceptibility in different part of the cardiac cycle Doctoral Thesis Columbia University New York 1934 Columbia University Press

45 Wiggers C J and Wegria R Ventricular fibrillation due to single localized induction and condenser shocks applied during the vulnerable phase of ventricular systole Am J Physiol 128 500 1971

46 Rossi M and Lown B The use of quinidine in cardioversion Am J Cardiol 19 234 1967

47 McCarthy C Varghese P J, and Barritt D W Prognosis of atrial arrhythmias treated by electrical countershock therapy A three year follow up Br Heart J 31 496 1969

48. Morris J J Peter R H and McIntosh H D Electrical conversion of atrial fibrillation Immediate and long term results and selection of patients Ann Intern Med 65 216 1966

49 Oram S, and Davies J P H Further experience of electrical conversion of atrial fibrillation to sinus rhythm Analysis of 100 patients Lancet 1 1294 1964

50 Szekely P Batson G and Stock D C Direct current shock treatment of cardiac arrhythmias Br Heart J 28 366 1966

51 Bjerkelund C and Orning M Evaluation of direct current hock therapy of atrial arrhythmias Acta Med Scand 184 481 1968

52 Vassaux C and Lown B Cardioversion of supraventricular tachycardia Circulation 39 791 1969

53 Rabbino M D Likoff W and Dreifus L S Complications and limitations of direct current counter shock JAMA 190 417 1964

54 Ross E M Cardioversion causing ventricular fibrillation Arch. Intern Med 114 811 1964

55 Castellanos, A Lamberg L Gilmore H and Johnson D Countershock exposed quinidine syncope Am J Med Sci 250 54 1965

56 Katz M J and Zitnik R J Direct current shock and lidocaine in the treatment of digitalis induced ventricular tachycardia Am J Cardiol 18 552, 1966

57 Lewis T Drury A N and Iliescu C C A demonstration on circus movement in clinical flutter of the auricles Heart 8 341 1921

58 Frithz G, and Aberg H Direct current conversion of atrial flutter Acta Med. Scand 187 271 1970

59 Brusca A De Francheschi A DiLeo M Nosenzo C, Gandolfo S and Marchisio O The electrical treatment of paroxysmal ventricular tachycardia Acta Cardiol 23 169 1968

60 Pennington J E Taylor J and Lown B Chest thump for reverting ventricular tachycardia N Engl J Med 283 1192 1970

61 Liberthson R R Nagel E L Hirschman J C Nussenfeld S R Blackbourne B D and Davis J H Pathophysiologic observations in prehospital ventricular fibrillation and sudden cardiac death Circulation 49 90 1974

62 Pantridge J F Adgey A A J Webb S W and Anderson J Electrical requirements for ventricular defibrillation Br Med J 2 313 1975

63. Pantridge J F Adgey A A J, and Webb S W The acute coronary attack, New York 1975 Grune & Stratton Inc p 66

64 Campbell N P S Webb S W, Adgey A A J and Pantridge J F Transthoracic ventricular defibrillation in adults Br Med J 2 13 9 1977

65 Crampton R S Low-energy ventricular defibrillation and miniature defibrillators (Letter) JAMA 235 2284 1976

Rickettsial vasculitis

David H Walker M D *
William D Mattern M D **
Chapel Hill N C

Important rickettsial diseases of man are distributed over all the continents with the exception of Antarctica In order to approach these diseases their etiologic agents must be defined taxonomically Definition of the term rickettsia varies from a nearly meaningless inclusiveness of almost any intracellular microorganism to a narrower consideration of only the genus *Rickettsia* In this discussion the other related genera *Coxiella* (Q fever) and *Rochalimaea* (trench fever) will be excluded Members of genus *Rickettsia* share the following characteristics gram negative bacterial ultrastructural morphology obligate intracellular parasitism ecologic niche including all or a portion of life spent in an arthropod host and serologic grouping relationships There are three serologic groups typhus group spotted fever group and scrub typhus group The concept that rickettsiae are an intermediate form of life between viruses and bacteria is completely outmoded That they are clearly a specialized group of bacteria is confirmed by method of replication (binary fission) content of both RNA and DNA ultrastructural morphology and sensitivity to antimicrobial agents Although rickettsiae are capable of penetrating and growing within a wide variety of host cells of various species and organ sources in man they are found only in vascular endothelium and in some diseases vascular smooth muscle This anatomic distribution determines the basically similar pathology (vasculitis) and pathophysiology (increased vascular permeability) of the rickettsial diseases

Geographic distribution of rickettsial diseases reflects the distribution of infected arthropod hosts and their contact with man Rickettsial diseases of man their etiologic agents vectors and geographic distribution are presented in Table I

Although other rickettsiae have been discovered in various econiches in the United States at this time only *Rickettsia rickettsii* (Rocky Mountain spotted fever) *Rickettsia mooseri* (murine typhus) *Rickettsia prowazeki* (recrudescent typhus) and *Rickettsia akari* (rickettsialpox) have been documented as etiologic agents of disease in man in recent times Evidence indicates that epidemic typhus has probably been transmitted to man from a natural zoonotic cycle of *Rickettsia prowazeki* in flying squirrels in the southeastern states and that *Rickettsia canada* possibly causes a disease similar to Rocky Mountain spotted fever [1] However in current reports Rocky Mountain spotted fever (RMSF) accounts for more than 90% of rickettsial disease with murine typhus a distant second in incidence and the others apparently quite rare [1]

The incidence of RMSF has risen to a high level with continued significant mortality In 19[illegible] only 199 cases were reported and by 1968 the annual total was still only 298 cases Since that time a remarkable increase has occurred peaking at a total of 1 153 cases in 1977 [2] Expressed as rates this is a rise from 0 11 cases per 100 000 population in 1959 to 0 50 cases per 100 000 nationally and 1 66 cases per 100 000 in the South Atlantic states in 1977 Although the mortality rate has fallen from 20% in the preantibiotic era it has remained in the 5 to 10% range to the present time despite the efficacy of tetracycline and chloramphenicol RMSF has been reported from

From the Depart[illegible] P[illegible] [illegible] [illegible] Medicine University of North Carolina S[illegible] [illegible] M[illegible] [illegible] [illegible] H[illegible] N C
Recei ed for publ[illegible]
Reprint requests D[illegible] [illegible] [illegible] [illegible] [illegible] [illegible]thology University of North Carolina S[illegible] [illegible] [illegible] [illegible] N C 2 514

*Dept. of Pathology [illegible] School of Medicine
**Dept. of Medicine [illegible] [illegible] School of Medicine

0002-8703/80/12089[illegible] + [illegible] [illegible] 1980 The C[illegible] V M[illegible] C[illegible]

McIntosh H The changes in cardiac output with reversion of atrial fibrillation to sinus rhythm Circulation 31 6 0 1965

10 Krohn B G and Magidson O Left ventricular ejection time following cardioversion Am J Cardiol 18 779 1966

108 Wright J S Fabian J and Epstein E J Immediate effect on cardiac output of reversion to sinus rhythm from rapid arrhythmias Br Med J 3 315 1970

109 Ikram H Nixon P G F and Arcan T Left atrial function after electrical conversion to sinu rhythm Br Heart J 30 80 1968

110 Rowlands D J Logan W F W E and Howitt E Atrial function after conversion Am Heart J 74 149 1967

111 Lo an W F W E Rowlands D J Howitt E and Holmes A M Left atrial activity following cardioversion Lancet 2 471 1965

112 Goldman M J Quinidine treatment of auricular fibrillation Am J Med Sci 222 382 1951

113 Goldman M J The management of chronic atrial fibrillation Indications for and method of conversion to sinus rhythm Progr Cardiovasc Dis 2 465 1960

114 Morris J J Jr Kong Y, North W C and McIntosh H D Experience with "cardioversion" of atrial fibrillation and flutter Am J Cardiol 14 94 1964

115 Hurst J W Paulk E A Jr Proctor H D and Schlant R C Management of patients with atrial fibrillation Am J Med 37 728 1964

116 Parsonnet V Pacemaker failure following external defibrillation (Letter) Circulation 45 1144 1972

117 Lau F Y Protection of implanted pacemakers from excessive electrical energy of DC shock Am J Cardiol 23 244 1969

118 Strom S Pericarditis following cardioversion A case report Acta Med Scand 195 431 1974

119 Berger R O Ocular complications of cardioversion Ann Ophthalmol 10 161 1978

120 Manelis G Transient left recurrent laryngeal nerve paralysis after cardioversion Harefuah 88 568 1975

121 Okel B B Vertebral fracture from cardioversion shock (Letter) JAMA 203 369 1968

122 Geddes L A Tacker W A Rosborough J P, Moore A G and Cabler P S Electrical dose for ventricular defibrillation of large and small animals using precordial electrodes J Clin Invest 53 310 19 4

123 Tacker W A Galioto F Guiliani E Geddes, L A and McNamara D G Energy dosage for human transchest electrical ventricular defibrillation N Engl J Med 290 214 1974

124 Tacker W A Defibrillation (Letter) JAMA 235 144 1976

125 Collins R E Giuliani E R Tacker W A and Geddes L A Transthoracic ventricular defibrillation Success and body wei ht (Abstr) Med In trum 12 53 19 8

126 Lown B Crampton R S DeSilva R A and Gascho J A The energy for defibrillation—too little or too much? N Engl J Med 298 1258 19 8

127 Kerber R E and Sarnat W Factors influencing the success of ventricular defibrillation in man Circulation 60 226 1979

128 Lappin H A Ventricular defibrillators in heavy patients N Engl J Med 291 153 1974

129 Tacker W A, Morris G C and Winters W L Transchest ventricular defibrillation of a subject weighing 102 5 kg South Med J 68 786 1975

130 DeSilva R A and Lown B Energy requirements for defibrillation of a markedly obese patient Circulation 57 827 19 8

131 Adgey A A J Ventricular defibrillation Br Heart J 40 119 19 8

13 Grace W J Kennedy R J and Nolte C T Blind defibrillation Am J Cardiol 34 115 19 4

133 Lown B and Taylor J "Thumpversion" N Engl J Med 283 1223 1970

134 Schott E Uber Ventrikelstillstand (Adams Stokes che Anfalle) nebst Bemerkungen uber andersartige Arhythmien passagerer Natur Dtsch Arch Klin Med 131 211 1920

135 Lown B and Axelrod P Implanted standby defibrillators, Circulation 46 637 1972

macules which are from less than one to five *millimeters in diameter blanch completely and* temporarily on pressure and are rarely tender Subsequently these lesions acquire a deep red to purple hue and increase in size even becoming confluent in some cases After 2 to 3 days from its onset the rash becomes nonblanchable and pete chial In severe cases during the third week necrosis of dependent peripheral parts including scrotum, prepuce, fingers toes and external ear may occur

Study of the pathologic lesions in rickettsial disease has been performed most comprehensive ly in epidemic louse borne typhus Wolbach who already had extensive experience in investigating RMSF was sent to Poland with the Typhus Research Commission during World War I His descriptions based on the study of skin from 36 necropsies and skin biopsies from 28 patients covered the range from the first day of rash to the twenty fourth day of disease [14] At the onset of rash (day 3 of disease) the only pathologic lesion was swelling of the endothelium of capillaries and small arteries and veins of the papillary and reticular dermis Rickettsiae were observed in swollen endothelial cells On day 5 of the disease arterioles and venules demonstrated mural thrombi overlying swollen endothelial cells which frequently contained numerous rickettsiae Peri vascular reaction was minimal Subsequently contiguous spread of rickettsiae with accumula tion of increased quantity of organisms was observed in serial sections, moreover the patho logic lesions involved larger vessels in the deep dermis and subcutaneous tissue and included more prominent perivascular mononuclear in flammation Dermal hemorrhages were observed around capillaries and vessels of pre capillary size on and after the eighth day of illness Organization of vascular thrombi was seen as early as the fifteenth day Areas of gangrene were demonstrated microscopically not to be accom panied by thrombosis of large vessels but to be due to thrombosis of capillaries and small arteries and veins beginning in the dermis and extending centripetally

Comparison of the lesions of typhus and RMSF is most remarkable for their similarity However differences which comprise more extensive de struction of the vascular wall including the media and less pronounced perivascular inflammation in RMSF reflect in ction of vascular smooth muscle by *Rickettsia rickettsii* and not *Rickettsia prowazeki* and the generally shorter course of fatal cases of RMSF

Rarely in any disease are the pathologic lesions correlated so closely with the clinical picture A careful study of the patient s clinical record will reveal a very close correlation between the microscopic findings and the physiologic dis turbances although the latter may be out of all proportion to the visible anatomic lesions." These comments by Harell in his review of RMSF in 1949 certainly apply to the physiologic distur bances in the peripheral circulation in the most severe rickettsial infections such as epidemic typhus scrub typhus and RMSF In 1944 Har rell referring to RMSF [15] and Woodward refer ring to epidemic typhus [16] postulated in separate publications that hypotension and circulatory collapse seen at the height of these rickettsial infections resulted not from cardiac weakness, but from peripheral circulatory failure the latter resulting from a decrease in blood volume as a consequence of an increase in systemic capillary permeability They both noted that the falling blood pressure at the height of the illness coin cided with the appearance of edema and with a fall in the concentration of serum proteins, partic ularly albumin

In a more detailed investigation of the patho physiology of the peripheral circulatory failure in RMSF, Harrell in 1949 reported serial observa tions in 13 patients [17] The entire natural history of the illness was observed since neither tetracy cline nor chloramphenicol was then available as specific treatment Sequential measurements of plasma volume (using Evans Blue dye) extra vascular volume (using thiocyanate space) and the serum concentrations of total protein albu min nonprotein nitrogen (NPN) and chloride were correlated with various clinical observa tions and the effect of intravenous therapy with crystalloid and colloid containing solutions was noted The illness was considered mild if the tourniquet test was negative there was no edema and the pulse and blood pressure were stable moderate if the tourniquet test was positive there was slight edema the pulse rate was increased and the patient appeared toxic and severe if there were purpura marked edema and delirium Cases with a fulminant clinical course were not included Data were summarized for the moder ate to severe cases at three stages (1) soon after

Table I

Disease	Etiology	Vector	Geographic distribution
Typhus group			
Epidemic typhus	*R prowazeki*	Louse	Historic all continents except Australia Recent Burundi, Rwanda Uganda Ethiopia Algeria Chad Niger Zambia Nigeria Zaire Liberia Bolivia Peru Ecuador Chile Guatemala Costa Rica Mexico
		Ectoparasite of flying squirrels	Southeastern U S
Recrudescent typhus	*R prowazeki*	None	Worldwide especially localities of previous typhus epidemics, eg Poland and Yugoslavia or countries of immigration of previous typhus cases eg U S and Canada
Murine typhus	*R mooseri*	Rat flea	Worldwide especially in warmer climates including U S
Spotted Fever group			
Rocky Mountain spotted fever	*R rickettsii*	Tick	U S especially southeastern states western Canada Brazil Colombia Mexico Panama
Old world tick borne spotted fever (Boutonneuse fever South African tick bite fever Kenya typhus etc)	*R conori*	Tick	Mediterranean basin Africa Asia
Siberian tick typhus	*R sibirica*	Tick	Siberia
Queensland tick typhus	*R australia*	Tick	Australia
Rickettsialpox	*R akari*	Mite	Probably worldwide documented in cities of U S and U S S R
Central European tick typhus	*R slovaca*	Tick	Central Europe Armenia
Scrub Typhus group			
Scrub typhus	*R tsutsugamushi*	Mite	Eastern and southern Asia and southwestern Pacific

states however there is a higher incidence in the southeastern states with North Carolina Virginia Tennessee Oklahoma South Carolina Georgia and Maryland reporting 66 1% of all cases between 1975 and 1977 Cases occur most often in children in males and between mid April and mid September Moreover mortality rates are higher for adults (over age 30 13 9% vs 5 4% under age 30) males (8 2% vs 4 5% in females) and nonwhites (13 9% vs 5 8% in whites)[6] Fatal cases seek medical attention at the same time during the course of illness as nonfatal cases However their rash appears later they give a history of tick bite less often or later in the course and initial or unexpected symptoms lead to misdiagnosis As a result of incorrect or delayed diagnosis antirickettsial treatment is not given or is given too late to be effective[7]

Effect of rickettsiae on the microcirculation

Dermal involvement in rickettsial diseases is not only a prominent clinical sign but also an opportunity to observe and evaluate the nature of the vascular events The observations indicate that the microcirculation is the primary target with variable subsequent contiguous centripetal extension to arteries and veins The temporal sequence of events which may be seen in the skin of patients with typhus and RMSF reflects the pathologic and pathophysiologic events in these diseases

The rash of RMSF is delayed usually occurring three days after onset of fever with a range of 2 to 7 days and rarely not appearing at all[8, 12] The rash tends to appear first on ankles feet wrists and hands and to spread centripetally to involve the entire body within 24 to 36 hours usually including the palms and soles This centripetal spread contrasts with the centrifugal spread of the rash of typhus The difference has never been satisfactorily explained although optimal growth of *Rickettsia rickettsii* at lower temperatures[13] would favor earlier attainment of a critical mass of pathogenic organisms in peripheral sites. Initially, the rash consists of pink unelevated

strated in the only case of fulminant RMSF with description of pathology reported in the literature.[2] In our case study of serial sections stained for fibrin histochemically and for *Rickettsia rickettsii* immunohistochemically demonstrated that thrombotic glomeruli were intensely infected and that nonthrombotic glomeruli were minimally or mildly infected. In an intermediate position, several recent cases with death occurring on day 6 or 7 of disease have had rare focal glomerular thrombi. These observations on thrombosis in renal tissue from rickettsial diseases indicate that thrombosis is the response to local injury to blood vessels by rickettsiae.

Two lesions which could be due to local and/or systemic effect of rickettsial infections are glomerulonephritis and edema of the kidneys. There is no consensus that glomerulonephritis actually occurs in rickettsial diseases. Glomerulonephritis was described by Allen and Spitz[23] in scrub typhus and RMSF. Ultrastructural examination of renal biopsies from five Brazilian cases of RMSF with various degrees of acute renal functional impairment demonstrated no glomerulonephritis with only nonspecific endothelial swelling and prominence of mesangial cells.[24] Our cases when studied by sections with controlled thickness (3 μm) and staining of basement membranes revealed no glomerulonephritis as judged by the absence of glomerular hypercellularity and basement membrane lesions. Another recent study[25] has shown no glomerular immune complexes by immunofluorescence and no ultrastructural deposits. On the other hand, increased renal weights, presumably secondary to edema, have been reported in some cases of scrub typhus[6] and RMSF.[1] This edema may result from multifocal vasculitis and/or acute tubular necrosis.

The significant pathologic lesion which is the effect of systemic shock on the kidneys is acute tubular necrosis (ATN). In two of 37 cases of typhus fever, heavy kidneys with pale, bulging cortices were compatible grossly with ATN.[11] Although ATN is not always identifiable morphologically in all of its time course and autolysis often renders tubular epithelium impossible to evaluate microscopically, the stage of ATN identifiable by markedly thin tubular epithelium and interstitial edema has been observed in cases of RMSF.[20, 23]

Renal pathophysiology in rickettsial diseases. With reference to [illegible] abnormalities of renal function, the remote effects of the systemic vasculitis far outweigh the effects of the observed intrarenal pathology and can best be understood as the sequential manifestations of altered systemic capillary permeability.[9] Interestingly, the basic renal lesion, a focal perivascular interstitial nephritis, finds little clinical expression. Early in the course of the more severe rickettsial infections, patients often present with dehydration, a moderately elevated BUN and serum creatinine concentration, mild hyponatremia and hypoproteinemia, a low normal blood pressure, and progressive hypovolemia. The BUN is often high in relation to the serum creatinine concentration, and the urine volume is reduced, though usually not to oliguric levels. There is a trace to 1+ proteinuria by reagent stick, and 24 hour collections contain less than 500 mg of protein. The urine sediment contains a few coarsely granular casts but no increase in cellular elements. The urine specific gravity is usually greater than 1.0[illegible] and urine sodium concentration is low, often less than 10 mEq/L. Expansion of intravascular volume with colloid or crystalloid solutions restores renal function to normal within a few days. This entire picture is consistent with prerenal azotemia.

At the height of illness in severe cases with a more protracted course, acute hypotension may precipitate oliguric acute renal failure (ATN). Despite prompt restoration of blood pressure to normal and maintenance of intravasular volume, the oliguria persists. The urine composition and sediment are typical of ATN. Recovery [illegible] ATN, in this setting has been reported in boutonneuse fever, a milder but related rickettsial infection,[27] but not to date in Rocky Mountain spotted fever, although the potential for recovery has been demonstrated. Oliguric acute renal failure is a regular occurrence in fulminant cases, in association with systemic circulatory collapse. Causes other than hypotension have been considered in the pathogenesis of ATN in Rocky [illegible] spotted fever, specifically non traumatic rhabdomyolysis with myoglobinuria, but evidence to support their occurrence is lacking.

As noted, histologic lesions of acute diffuse glomerulonephritis were described in one early report of RMSF. A review of published cases and our own material, however, does not reveal o[illegible] documentation of this lesion, and there is no clinical data (heavy proteinuria, hematuria

onset of the rash (2) at the height of illness 9 to 14 days after onset of the rash and (3) during the recovery period in the third week after onset of the rash

Patients presented shortly after the appearance of the rash with clinical signs of dehydration an elevated NPN and low serum chloride concentration a normal or slightly low serum protein concentration and plasma volume a normal thiocyanate space and a low normal blood pressure When intravenous therapy with crystalloid solutions was given in an effort to correct the dehydration at this point in the illness there was a prompt fall in the NPN and a rise in serum chloride concentration Plasma volume rose transiently and there was a reciprocal fall in the serum protein concentration If crystalloid solutions were continued the expansion of plasma volume was sustained and there was a striking rise in the thiocyanate space coinciding with the development of progressive peripheral edema

At the height of the illness the onset of hypotension was associated with a more marked reduction in the serum protein concentration and plasma volume elevated thiocyanate space and peripheral edema Crystalloid administration at this point accelerated the extravascular accumulation of fluid without a favorable effect on the blood pressure or plasma volume

The onset of recovery was marked by return of temperature to normal and a reversal of the above abnormalities The blood pressure rose to normal as plasma volume began to increase The thiocyanate space gradually decreased as edema was mobilized and diuresed and finally the serum protein concentration returned to normal The administration of colloid solutions such as plasma or albumin in contrast to crystalloids did support the blood pressure and plasma volume at the height of illness and early in the recovery period but in five of the six instances reported its administration also precipitated acute pulmonary edema These findings were interpreted to indicate that the vasculitis of RMSF led to a progressive increase in systemic capillary permeability such that there was a gradual loss of protein from the vascular compartment and a decrease in intravascular oncotic pressure Although this study served to characterize the sequential changes in systemic capillary permeability in the more severe cases it left unanswered important questions about fluid therapy and also raised basic questions about cardiac function and pulmonary capillary function in RMSF

Renal pathology in rickettsial diseases The pathologic lesions of kidneys in rickettsial diseases may be considered to be either of two types lesions due to local effects of rickettsiae on renal vessels or lesions due to the effects of systemic hypovolemic shock In studies of typhus fever Wolbach described focal lesions in which only small blood vessels are affected and the cellular response is infiltrative These lesions contained capillaries or precapillary blood vessels surrounded by mononuclear phagocytes lymphocytes plasma cells and polymorphonuclear leukocytes and incorporated one or several tubules in various stages of injury up to actual necrosis Wolbach noted that these lesions were present also in scrub typhus and Rocky Mountain spotted fever but that in all three diseases the distribution was spotty and little renal parenchyma was involved[1] In the classic description of the pathology of RMSF Lillie observed that 12 of 17 cases had focal lesions with irregular interstitial and perivascular infiltration by lymphocytes in later cases often plasma cells and large lymphoid cells as well These lesions were especially marked at the corticomedullary junction Focal pericapillary and interstitial hemorrhages were identified in six cases Our study confirmed these observations and demonstrated by specific immunofluorescence that the distribution of the majority of the *Rickettsia rickettsii* was identical with that of the multifocal perivascular interstitial nephritis concentrated near the corticomedullary junction[20]

Another potential local effect of rickettsial infection on the kidney is thrombosis Wolbach described precisely this relationship in typhus fever with thrombosis of vessels in the focal interstitial lesions no lesions of large blood vessels and one case with small mural thrombi in small arteries of the pelvic submucosa with rickettsiae in the endothelium of the affected vessels[11] Our original study of ten cases of RMSF with histochemical staining for fibrin revealed thrombi only in vessels of a minority of the focal interstitial lesions and no glomerular thrombi[20] Subsequently we have investigated a case of fulminant RMSF (defined by Parker[21] as fatal within 3 to 5 days of onset) which showed fibrin thrombi in approximately half of the glomeruli Glomerular fibrin thrombi were also demon

nine cases[3] Absence of left ventricular dilatation indicated that severe myocardial failure was not the etiology of hypotension shock and death in these cases of RMSF

Pathologic studies of lung in rickettsial disease have demonstrated interstitial pneumonitis with alveolar walls containing mononuclear leukocytic infiltration[14 18 19 23 26 29 33] In cases which were not complicated by bronchopneumonia interstitial pneumonitis was manifested grossly by congestion and edema Further microscopic evidence for loss of vascular integrity are multiple foci of alveolar hemorrhage fibrin and edema Examination of lungs from cases of RMSF by specific immunofluorescence has revealed moderate to severe infection of the pulmonary microcirculation by *Rickettsia rickettsii* (see illustrative Case 2 below) thus providing a pathogenetic explanation for the interstitial pneumonitis and the increased pulmonary vascular permeability[33]

Cardiovascular and pulmonary pathophysiology in rickettsial diseases The studies already referred to convincingly exclude any significant contribution by the heart to the development of hypotension and peripheral circulatory collapse in the course of severe rickettsial infection but the role of the heart in the development of pulmonary edema a less common complication has been more difficult to clarify In his classic study of the typhus heart Woodward documented the fact that central circulatory failure and pulmonary edema were distinctly uncommon None of the 30 severely or critically ill patients he studied during the course of their illness had cardiac enlargement by physical examination a gallop rhythm distended neck veins or an enlarged liver He recorded serial measurement of venous pressure Values above 12 cm water were not seen and the average value was 8 cm water Radiographs were available in 12 patients and showed neither cardiomegaly nor pulmonary conjestion Electrocardiograms showed no striking deviations from normal Rales were heard frequently but usually in association with coarse rhonchi and were considered to be manifestations of tracheobronchitis or patchy bronchopneumonia both of which were often observed at necropsy

Pulmonary edem [illegible] h [illegible] nally been noted in scrub typhu [illegible] u [illegible] njunction with other findings of [illegible] he patients were critically ill or [illegible] the pulmonary edema was considered to be a manifestation severe rickettsial pneumonitis[6]

Pulmonary edema has been most frequently reported in RMSF and its pathogenesis is critical importance with regard to fluid ment A careful review of the case reports of the 13 patients Harrell originally described in study of peripheral circulatory failure re that five developed pulmonary edema during course of their illness[17] The episodes of nary edema all occurred in the second week of illness at the height of the changes in syste capillary permeability or a few days into th recovery period The administration of solutn containing colloid immediately preceded development of pulmonary edema in instance and an increase in plasma documented by the Evans Blue dye Distended neck veins were not observed howe and the one recording of venous pressure d an episode of pulmonary edema revealed a va of 10 cm H_2O A gallop rhythm was noted in one instance Treatment consisted of d administration and fluid restriction There clinical resolution of the pulmonary edema in 48 hours in four of the patients but the fi patient developed bacterial pneumonia died

A recent clinical study of the pulmonary ifestations in RMSF confirms and extends the observations[34] The records of all patients hospital documented to have RMSF betwe 1973 and 1976 were reviewed Nine of the patients had deterioration in pulmonary fu co during the first week of hospitalization with widening of the alveolar arterial oxygen d ence Seven developed radiographic infil and six developed pulmonary edema All were in markedly positive fluid balance and had received large amounts of fluid fol hypotensive episodes None of the patients third heart sounds cardiac enlargement ra graphically or electrocardiographic chan es of the patients with severe disease died within hours of hospitalization Diuresis in the o eight patients led to prompt improvement of exchange Radiographic and clinical gas pulmonary edema cleared within 48 hours

Since 1976 we have seen two additional one which illustrates the clinical presentation pulmonary involvement in RMSF and the which highlights the pathological changes

red cell casts) to support the occurrence of acute glomerulonephritis

Thus the major clinical abnormalities in renal function prerenal azotemia and ATN are the early or later consequences of the systemic vasculitis Recovery of renal function with prerenal azotemia is the rule and the potential for recovery from ATN with resolution of the vasculitis is suggested

Cardiovascular and pulmonary pathology in rickettsial diseases In general the heart in typhus fever RMSF and scrub typhus manifests negligible gross alterations and virtually universal microscopic interstitial mononuclear myocarditis Wolbach felt that inflammatory infiltration of the myocardium was diffuse because of its relationship to the most diffusely distributed blood vessels the capillaries that the order of severity of inflammatory infiltration was scrub typhus typhus and RMSF and that not much evidence of degeneration of heart muscle could be demonstrated[16] Myocarditis was noted in a series of eight autopsies of cases of RMSF by Wilson and Chowning in 1904[8] They noted a few epicardial petechiae dark fluid blood filling the right ventricle empty left ventricle and considerable round cell infiltration Following a number of case reports by a series of authors often citing myocarditis Lillie published the classic description of myocarditis in RMSF in his series of 17 cases[19] Grossly he noted that the right ventricle was more often dilated than the left but in the majority the status of the chambers was normal or contracted and that altogether gross changes were slight Microscopically two cases were normal 15 manifested interstitial infiltration of variable density chiefly by lymphocytes often with lesser numbers of plasma cells monocytes a few neutrophil or eosinophil leukocytes or mast cells Myocarditis was irregular and patchy often distinctly centered about small vessels and in interfascicular connective tissue Only two cases had focal coagulative necrosis of myocardial cells

In the definitive study of the pathology of typhus Wolbach stated that as a rule the left ventricle was contracted and the right moderately dilated[4] In six postmortem examinations performed soon after death in cases without significant bacterial complications myocardium showed pallor loss of consistency and yellowish streaks and points Acute valvular lesions and macroscopic mural thrombi were not detected Microscopic lesions which were observed in all 37 necropsies included slight degrees of edema focal and diffuse myocarditis with interstitial macrophages lymphocytes plasma cells few polymorphonuclear leukocytes and vascular lesions almost wholly restricted to capillaries and vessels of pre capillary size Large blood vessels in the heart and pericardium very rarely contained lesions Pathologic studies of the heart in scrub typhus have yielded essentially the same observations as in typhus fever and RMSF[26]

Besides myocarditis there have been few consistent pathologic alterations of the heart in the rickettsial diseases When present they have included few subendocardial mononuclear inflammatory foci pericardial fluid varying from none to moderate to rarely large amounts and an occasionally demonstrated focal inflammatory lesion involving a conduction bundle[3] or the Purkinje conduction system

The relationship of rickettsiae to the myocarditis has been unclear Much of this unsatisfactory state has been a result of the unreliability of the various Giemsa techniques to demonstrate rickettsiae Even in the hands of Wolbach who used the method to demonstrate rickettsiae successfully in many lesions of typhus and spotted fever rickettsiae could not be satisfactorily demonstrated in heart lesions of typhus fever Of 40 cases of RMSF in which Giemsa stain was reported to have been used to search for rickettsiae in heart only a single case was reported to contain rickettsiae within the cytoplasm of the endothelial cells of the subepicardial and interstitial capillaries[31] In contrast *Rickettsia rickettsii* were demonstrated in hearts of all eight untreated or inadequately treated cases of RMSF which were examined by a technique of deparaffinization trypsin digestion and specific direct immunofluorescence in our laboratory[32]

Rickettsia rickettsii were observed in capillaries venules arterioles and large vessels including coronary arteries in descending order of involvement Vascular infection with resultant vascular injury and increased permeability provides the probable pathogenetic mechanism for moderate myocardial edema Data on the same series of hearts with etiologically confirmed RMSF which suggested myocardial edema were increased heart weight in eight of nine cases and detectably increased interstitial volume in six of

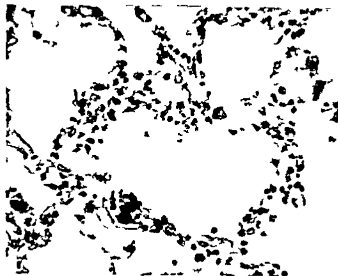


Fig 2 Photomicrograph of lung from Case 2 of RMSF Interstitial pneumonia is characterized by mononuclear cell infiltration of the alveolar septa Proteinaceous edema fluid fills the alveolar spaces (Hematoxylin-eosin stain original magnification ×220)



Fig 3 Photomicrograph of lung from Case ? of RMSF Brightly immunofluorescent *Rickettsia rickettsii* are vis within thickened portions of an alveolar septum (Flu resce isothiocyanate conjugated anti *Rickettsia rickettsii* glob fraction original magnification ×3?0)

respiratory infection was diagnosed and treated symtomatically Over the next two days she developed nausea vomiting high fever and malaise Physical examination at the time of admission showed a blood pressure 80/60 mm Hg and a pulse rate of 100 beats per minute She was oriented though lethargic and appeared acutely ill Physical examination showed no rash Scleral icterus was noted but without enlargement or tenderness of the liver The lungs were clear to auscultation and no signs of heart failure were observed Liver function tests were markedly abnormal with total bilirubin 15 mg/dl moderately elevated alkaline phosphatase and markedly elevated liver enzyme values The BUN was 91 mg/dl and serum creatinine was 4 8 mg/dl The serum sodium was 125 mEq/L serum calcium 6 8 mg/dl total protein 5 8 g/dl and albumin 3 1 g/dl Febrile agglutinins included a Proteus OX 19 titer of 1 20 Fluids were given as 5% dextrose in water alternating with normal saline at a rate of 3 000 ml per day and methylprednisolone was given intravenously 1 gm every 8 hours The blood pressure rose initially but she remained oliguric and her general condition deteriorated Thirty six hour after admission therapy with tetracycline was begun intravenously 500 mg every 8 hours Forty six hours after admission the patient became tated and hypotensive Two hours later a ardiorespiratory arrest occurred following an episode of vomiting the patient could not be resuscitated

Pertinent necropsy findings were multifoca interstitial pneumonitis bilateral pulm ma (Fig 2) associated with severe ricketts infection of alveolar capillaries (Fig 3) m mononuclear interstitial myocarditis and acu tubular necrosis with cortical interstitial ede and low regenerative tubular epithelium

Comment Although lacking extensive pulmo nary clinical and functional data this patient an excellent example of the pathologic and rick ettsiologic involvement of lungs heart and kid neys in RMSF Despite initiation of tetracycl treatment on her fourth day of illness she su cumbed to a severe rickettsial infection As su gested clinically by the persistent oliguria follow ing restoration of blood pressure to normal w intravenous fluids she had acute tubular at autopsy One of the most important manifesta tions of her disease was severe rickettsial infectio of the pulmonary microcirculation with alveolar edema Pulmonary edema w documented grossly and microscopically in face of only mild mononuclear interstitial myo carditis

Based on the pathological changes we h described in the heart and lungs and the lim clinical data referred to above it appears that pulmonary edema seen in RMSF is most o

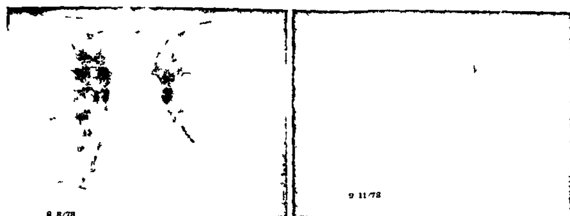


Fig 1 Chest radiographs in Case 1 of RMSF On the day of admission (left) heart size and pulmonary vascular pattern are normal After two days of parenteral fluid administration (right) heart size is unchanged but radiologic pattern of pulmonary edema is present

lustrative cases

Case 1 A 48 year old white housewife from mithfield N C removed a tick from her scalp n days before admission Three days later she eveloped severe headache nausea and fever hereafter she had daily fevers of 40 C and ntermittent vomiting Three days before admis on a red macular rash was noted on the trunk nd extremities including the palms and soles he was admitted to North Carolina Memorial ospital on September 8 1978 Physical examina on showed a blood pressure of 140/80 mm Hg nd a temperature of 40 C Pulse rate was 100 eats per minutes She was oriented and alert but ppeared weak and acutely ill A generalized aculopapular rash with petechial areas was oted on the trunk and extremities The lungs ere clear the neck veins were not distended and xamination of the heart showed no enlargement r gallop rhythm There was no peripheral edema o adenopathy and the neurological examination as normal Blood chemistries included sodium 33 mEq/L BUN 15 mg/dl creatinine 0 8 g/dl calcium 8 6 mg/dl total protein 6 5 /dl and albumin 3 5 g/dl The hematocrit was % and the platelet count 92 000/µl The pro rombin time and partial thromboplastin times ere normal The initial chest radiograph (Fig 1) as interpreted as normal A skin biopsy on the ay of admission examined by specific direct nmunofluorescence was diagnostic for Rocky Iountain spotted fever with *Rickettsia rickettsii* n dermal blood vessels

She was begun on treatment with intravenous hloramphenicol 100 mg every 8 hours and intravenous hydration with 5% dextrose in normal saline at a rate of 75 ml/hr On the second day after admission she developed progres sive shortness of breath over a period of several hours Examination revealed diffuse rales but the neck veins were not distended and no gallop rhythm was heard The blood pressure was 160/80 mm Hg Arterial blood gases revealed pH 7 52 PCO 22 torr and PO 30 torr Repeat serum total protein was 6 5 g/dl with albumin 3 0 g/dl The electrocardiogram showed sinus tachycardia and nonspecific ST segment changes A repeat chest radiograph was interpreted as showing pulmo nary edema (Fig 1) She was transferred to the intensive care unit where she was treated with oxygen furosemide and digoxin Within three days pulmonary gas exchange had improved and the rales and pulmonary infiltrate on chest radio graph had cleared Her recovery was unevent ful

Comment Fluid administration in this other wise stable patient led to the abrupt development of pulmonary edema in the absence of signs of heart failure or elevated systemic venous pres sure The predominance of infiltrates in the upper lobes is similar to that seen when pulmonary capillary wedge pressure is elevated—i e in car diogenic pulmonary edema—but might have occurred at only slightly increased pulmonary capillary wedge pressure in the presence of both a decreased intravascular oncotic pressure and altered pulmonary capillary permeability

Case 2 A 19 year old black female from Rock Hill S C was seen by her physician two days prior to hospitalization at which time an upper

14 Wolbach S B Todd J L and Palfrey F W Pathology of typhus in man *in* The Etiology and Pathology of Typhus Being the Main Report of the Typhus Research Commission of the League of Red Cross Societies of Poland Cambridge 1922 Harvard University Press, pp 152 256

15 Harrell G T Venning W and Wolff W A The treatment of Rocky Mountain spotted fever with particular reference to intravenous fluids J A M A **126** 929 1944

16 Woodward T E and Bland E F Clinical observations in typhus fever J A M A **126** 287 1944

17 Harrell G and Aikawa J Pathogenesis of circulatory failure in Rocky Mountain spotted fever Arch Intern Med **83** 331 1949

18 Wolbach S B The pathology of the Rickettsial diseases of man *in* Moulton F R ed Rickettsial Diseases of Man Washington 1948 American Association for the Advancement of Science pp 118 125

19 Lillie R D The pathology of Rocky Mountain spotted fever Natl Inst Health Bull **177** 1 1941

20 Walker D H and Mattern W D Acute renal failure in Rocky Mountain spotted fever Arch Intern Med **139** 443 1979

21 Parker R R Rocky Mountain spotted fever J A M A **110** 1185 1938

22 Moon J H and Silverberg S G Febrile exanthem in 14 year-old boy with subsequent development of coagulopathy Va Med Monthly **98** 271 1971

23 Allen A C and Spitz S A comparative study of the pathology of scrub typhus (tsutsugamushi disease) and other rickettsial disease Am J Pathol **21** 603 1945

24 de Brito T Tiriba A Godoy C V F Penna D O and Jordao F M Glomerular response in human and experimental rickettsial disease (Rocky Mountain spotted fever group) A light and electron microscopy study Path Microbiol (Basel) **31** 365 1968

25 Bradford W D, Croker B P and Tisher C C Kidney lesions in Rocky Mountain spotted fever a light immunofluorescence and electron microscopic study Am J Pathol **97** 381 1979

26 Levine H D Pathologic study of thirty one cases of scrub typhus fever with especial reference to the cardiovascular system AM HEART J **31** 314 1946

27 Gutman A Taragan R Bernheim J et al Acute renal failure in spotted fever Harafuah **89** ?98 1975

28 Wilson L B and Chowning W M Studies in Pyrou... mosis hominis (spotted fever or tick fever of t... Rocky Mountains) J Infect Dis **1** 31 1904

29 Settle E B Pinkerton H and Corbett, A J ... pathologic study of tsutsugamushi disease (scrub typh... with notes on clinicopathologic correlation J Lab Cl... Med **30** 639 1945

30 Bradford W D and Hackel D B Myocardial invo... ment in Rocky Mountain spotted fever Arch... Lab Med **102** 357 1978

31 Pincoffs M C and Shaw C C The eastern type ... Rocky Mountain spotted fever Report of a case ... demonstration of rickettsiae Med Clin North A... **16** 1097 1933

32 Walker D H Paletta C E and Cain B G Pathog... esis of myocarditis in Rocky Mountain spotted fe... Arch Pathol Lab Med **104** 171 1980

33 Walker D H Crawford C G and Cain B G Ricke... sial infection of the pulmonary microcirculation, t... basis of interstitial pneumonitis of Rocky Mou... spotted fever Human Pathology **11** 263, 1980

34 Donohue J F Lower respiratory tract involvement ... Rocky Mountain spotted fever Arch Intern ... **140** 223 1980

35 Walker D H Cain B G and Olmstead P ... Laboratory diagnosis of Rocky Mountain spotted ... by immunofluorescent demonstration of *Rickettsia ric... ettsii* in cutaneous lesions Am J Clin Pathol **69** ... 1978

36 Woodward T E Pedersen C E Jr Oster C ... Bagley L R Romberger J and Snyder M J Pro... confirmation of Rocky Mountain spotted fever Iden... cation of rickettsiae in skin tissues, J Infect D... **134** 297 1976

37 Fein A Grossman R F Jones J G Overland ... Pitts L Murray J F and Staub N C The ... edema fluid protein measurement in patients w... pulmonary edema Am J Med **67** 32 1979

38 Shoemaker W C and Hauser C J Critique ... loid versus colloid therapy in shock and shock ... Critical Care Med **7** 117 1979

39 Stein L Beraud J Morissette M daLuz P Weil ... H and Shubin H Pulmonary edema du... infusion Circulation **52** 483 1975

non cardiogenic It typically occurs after vigorous fluid administration usually at the height of illness and is probably a consequence of an increase in pulmonary capillary permeability Confirmation of the pathogenesis of the pulmonary edema however will require more specific physiologic data including measurements of pulmonary capillary wedge pressures pulmonary capillary oncotic pressures and pulmonary interstitial oncotic pressures as estimated by the measurement of edema fluid protein concentration[3]

Conclusions

The documented changes in systemic capillary permeability and probable changes in pulmonary capillary permeability which we have discussed have definite therapeutic implications with reference to intravenous fluid therapy in severely affected patients The selection of fluids either colloids or crystalloids is particularly controversial in terms of predicting the effect on the *Starling forces* in the pulmonary circulation The use of crystalloids may cause both a small increase in intravascular hydrostatic pressure (PCWP) and by dilution a small decrease in intravascular oncotic pressure The net change in filtration pressure may be sufficient to favor transudation of fluid into the pulmonary interstitium Colloid administration may cause an increase in pulmonary intravascular hydrostatic and oncotic pressures but interstitial oncotic pressure may also rise if pulmonary capillary permeability to proteins is sufficiently altered favoring the development of pulmonary edema As noted five of the 13 patients reported by Harrell developed pulmonary edema after colloid was administered at the height of the illness

Among the conclusions that can be reached with certainty is the fact that pulmonary function is particularly at risk in severe RMSF Patchy areas of vasculitis and interstitial edema in the kidney or heart may cause little damage to renal tubular transport or myocardial contraction and in the systemic circulation may not impair flow or peripheral delivery of nutrients (at least until hypotension supervenes) These same pathologic changes in the pulmonary capillaries on the other hand may lead to an acute increase in lung water and impairment of gas exchange

The purpose of fluid administration in severe rickettsial infections is to expand intravascular volume and support blood pressure so that adequate perfusion of vital organs and peripheral tissues can be maintained during the acute phase of the vasculitis Care should be exercised to limit fluid administration (1) to avoid the accumulation of peripheral edema with the attendant risk of subsequent intravascular volume overload as vascular integrity is restored and (2) to minimize the risk of developing pulmonary edema particularly at the height of the illness when pulmonary capillary permeability may be significantly increased Monitoring of pressures in the pulmonary capillary circulation should be considered in the severely ill patient with hypotension to assist in the selection and use of intravenous fluids

The authors wish to thank Ms Barbara G Cain for [illegible] raphic assistance Mrs Jennie Lu Hollander for secretarial assistance and Dr James Maynard for providing Case 2 [illegible] ou tud

REFERENCES

1 Weiss E Growth and physiology of rickettsiae Bacteri Rev 37 59 1973
2 Bozeman F M Masiello S A Williams M S and Elisberg B L Epidemic typhus rickettsiae isolated from flying squirrels Nature 255 545 1975
3 Bozeman F M Elisberg B L Humphries J W Runcik K and Palmer D B Jr Serologic evidence of *Rickettsia canada* infection of man J Infect Dis 121 3[illegible] 19 0
4 Annual Summary 1977 Morbidity and Mortality Weekly Report HEW Pub No (CDC) 78-8241 26 ? 19 8
D Angelo L J Winkler W G and Bregman D J Rocky Mountain potted fever in the United States 1975 19 7 J Infect Dis 138 ?73 1978
6 Hattwick M A W, O Brien R J and Hanson B F Rocky Mountain spotted fever epidemiology of an increasing problem Ann Intern Med 84 ?32 19 6
7 Hattwick M A W Retailliau H, O'Brien R J Slutzker M, Fontaine R E and Hanson B Fatal Rocky Mountain spotted fever J A M A 240 1499 19 8
8 Maxey E E Some observations on the so-called spotted fever of Idaho Medical Sentinel 7 433 1899
9 McCullough G T Spotted fever Medical Sentinel 10 225 1902
10 Wolbach S B Studies on Rocky Mountain spotted fever J Med. Res. 41 1 1919
11 Peterson J C Overall J C, and Shapiro J L Rickettsial diseases of childhood A clinical pathologic study of tick typhus Rocky Mountain spotted fever" and murine typhus "endemic typhus" J Pediatr 30 495 1947
12 Harrell G T Rocky Mountain spotted fever Medicine 28 333 1949
13 Stoenner H G Lackman D B and Bell E J Factors affecting the growth of rickettsias of the spotted fever group in fertile hens eggs J Infect Dis. 110 1?1 1962

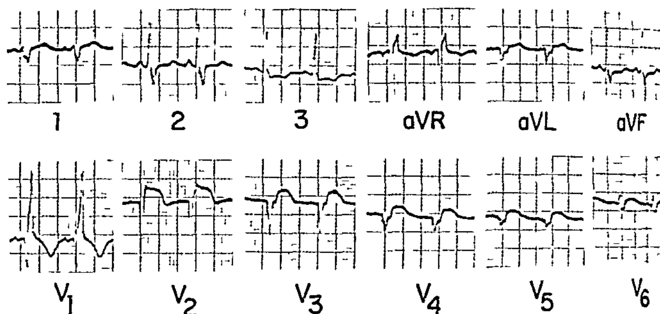


Fig 1 Electrocardiogram on admission with sinus rhythm right axis deviation right bundle branch block, and pathologic Q waves with ST elevation in Leads 1 L, and V to V

positive for MB fraction Swan Ganz catheteriza tion showed a cardiac output of 4 6 liters/minute a cardiac index 3 11/min /M and a pulmonary capillary wedge pressure of 18 Over the first three days in hospital she also developed bibasilar rales an increase in heart size by radiograph and a rise in her pulmonary capillary wedge pressure to 30 Her pericardial friction rub resolved by 48 hours She was treated with digoxin and furosemide and continued on aspirin for pericarditis and fever

Other laboratory studies showed an elevated sedimentation rate (62 mm by the Wintrobe method) a negative rheumatoid factor and lupus erythematosus preparations normal serum pro tein electrophoresis and immunoglobulin C3 and C4 and an antinuclear antibody titer of 1 80 Thallium myocardial perfusion imaging revealed anteroseptal and apical defects Gated blood pool scan showed little or no motion of the anterior wall and an ejection fraction of 35% No pericar dial effusion was noted on the echocardiogram Over a seven day period her ECG showed loss of R waves anteriorly and a resolution of the ST changes

On the eleventh hospital day cardiac catheter ization was performed Coronary angiography showed a normal left main coronary artery and a proximal left anterior descending coronary artery which was totally occluded in its proximal course There was some left to left collateral filling at the distal LAD The remainder of the coronary tree was entirely normal (Fig 2) A left ventricul was entirely normal (Fig 2) A left ventricu gram done in the RAO and LAO projectio showed a mildly dilated left ventricular chamber mitral regurgitation fair over all contractil but an akinetic segment involving mid anter wall apex and the distal inferior wall (Fig 3) Left ventricular end diastolic volume was 123 ml stroke volume was 32 ml and calculated ejectio fraction was 26% Left ventricular end-diastolic pressure after contrast injection was 30 mm H His bundle studies showed a normal A H and H V time

Post hospital course

DR DAVID BLUMENTHAL The patient's subse quent recovery was uneventful and she was discharged on digoxin 0 25 mg per day One month later she was admitted to evaluate la anterior chest pain similar to that experienced with the prior acute infarction At that time she had a diffusely palpable point of maximal impulse a right pleural effusion bibasilar ra and mild hepatomegaly Her electrocardiogram was unchanged Six days after admission she was discovered unresponsive pulseless apneic and in ventricular fibrillation Immediate cardiopul monary resuscitation was initiated and was suc cessful The subsequent hospital course was complicated by ventricular tachycardia which

Clinical pathologic conference

Delayed acute myocardial infarction after blunt chest trauma in a young woman

Stephen C Vlay M D
David S Blumenthal M D
Dolores Shoback M D
Kim Fehir M D
Bernadine H Bulkley M D
Baltimore Md

Case presentation

DR KIM FEHIR The patient was a 25 year old woman who was in entirely good health until five days before presenting to hospital when she was involved in an automobile accident in which her car was thrown into a spin and she struck her forehead and chest on the steering wheel She was treated in a nearby hospital emergency room for local chest bruising and tenderness chest and skull radiographs were normal Mild dyspnea on exertion developed at home and five days post trauma when she suddenly developed a persistent squeezing substernal chest pain accompanied by nausea vomiting and cold diaphoresis After 24 hours of pain she presented to the hospital complaining of substernal chest pain and also sharper pain aggravated by breathing

Her past medical history was remarkable for a five year history of heroin abuse for which she was taking methadone She was on no other medication had never taken oral contraceptives and was not recently pregnant Her only cardiovascular risk factor was a 24 pack year history of smoking

Initial physical examination revealed a moderately distressed young woman complaining of chest pain Pertinent physical findings included a blood pressure of 130/86 mm Hg without pulsus paradoxus a regular pulse of 96 and normal respirations Her chest wall showed no local bruising or tenderness Her lungs were clear without rales rhonchi rubs or wheezes On cardiac examination the point of maximal impulse was in the fifth intercostal space midclavicular line Her heart sounds were normal a soft ventricular gallop (S) and a pericardial friction rub was present There were no murmurs thrills carotid bruits jugular venous distention hepatojugular reflux hepatosplenomegaly cyanosis clubbing or peripheral edema

The chest radiograph showed a normal cardiac silhouette with a cardiothoracic ratio of 12/25 the electrocardiogram (Fig 1) showed normal sinus rhythm right axis deviation right bundle branch block and pathologic Q waves with ST elevation in Leads I L and V_1 to V_4 compatible with an acute anterior wall myocardial infarction Her initial creatine kinase (I U) was 2 390 and the remainder of her laboratory findings were unremarkable

Hospital course

DR DOLORES SHOBACK Her hospital c was initially complicated by the develc complete heart block requiring a t transvenous pacemaker for a period of five after which normal sinus rhythm returned creatine phosphokinase (CK) every four hours showed subsequent 2 080 1 930 1 760 650 and 588 which

From the C d ascula D visi n of th D p rtm nt f Medicine a d the Departm nt of P th l gy The J hn Hopk ns M d l Inst t tions, Baltim re Md

S pported in part by G nts 5T 3? HL-072?7 03 and P50 HL 1 655 04 from the N ti nal H art, Lung and Blood Institute Nation l Inst tutes (H th

Recei ed for publi ati n Ma ch 3 1980

Reprint req ests Bern dine H Bulkley M D C rnegie 568 Card vascular D is n The Johns Hopkins Hosp tal B ltim re Md 21205

00? -8 03/80/1?090? + 10$01 00/0 © 1980 The C V Mosby Co

Table I

Author date	Patient Age	Patient Sex	Etiology of blunt trauma	Coronary artery involved	ECG
Warburg 1940	59	M	Run over by bicycle fell on chest	LAD	
MacDonald 1941	21	M	Struck in chest by softball	LAD	
Jokl et al 1944	10	M	Struck in chest during boxing match	LAD	
Hedinger 1948	53	M	Kicked in chest by horse with fracture of sternum	LAD	
Levy 1949	49	F	Auto accident struck chest on front seat	LAD	Anteroseptal MI
Lehmus et al 1953	62	M	Auto accident struck chest on dashboard	LAD	
Stewart 1967	42	M	Struck by piece of wood recoiling from circular saw	LCfx	Posterolateral MI subsequent development RBBB
Harthorne 1967	32	M	Struck in chest during barroom brawl	RCA	Inferior wall MI
Heyndrickx et al 1974	62	M	Auto accident struck chest	RCA	Inferior wall MI complete heart block
Stern et al 1974	16	M	Auto accident struck chest on steering wheel	LAD	RBBB anterior wall MI
Oren et al 1976	35	M	Struck in chest by fist	LCfx	Inferior and posterior MI
de Feyter et al 1977	36	M	Struck in chest by football	LAD	Anterior wall MI
Candell et al 1979	38	M	Auto accident struck chest	LAD	Anteroseptal MI left axis deviation
	44	M	Auto accident struck chest	RCA	Inferior wall MI complete heart block
Oliva et al. 1979	17	F	Auto accident struck chest on steering wheel	RCA	Inferior wall MI
Present Case	25	F	Auto accident struck chest on steering wheel	LAD	RBBB anterior wall MI

Abbreviations F = female LAD = left anterior descending coronary artery M = male MI = myocardial infarction RBBB = right bundle branch block RCA = right coronary artery

ventricular pacing failed to elicit ventricular tachycardia

Five months after the original infarction the patient died suddenly while driving an automobile On her prior clinic visit she claimed to have taken her digoxin and procainamide faithfully

Clinical discussion

DR STEPHEN VLAY It is likely that this young woman's myocardial infarction was somehow related to the chest trauma which occurred one week before her occlusion Nonpenetrating trauma to the chest may injure almost any portion of the heart resulting in myocardial contusion, pericardial aneurysm or rupture There may be valvular injury or the trauma may bring about valvular dysfunction due to laceration or rupture of the valves Occlusion of a major coronary artery as a direct result of blunt trauma has been regarded as rare, and has been reported only in the presence of preexistent coronary artery disease In their series of 546 autopsy cases of nonpenetrating cardiac trauma Parmley and colleagues reported no instances of coronary occlusion although they



Fig 2 *Left* In the right anterior oblique (RAO) proje ti n l ft anterior descending coronary artery is occluded proximally *(arrow)* immediately after the takeoff of he f r t LAD diag nal branch The left circumflex system is normal. *Right* The RCA system is free of di ease

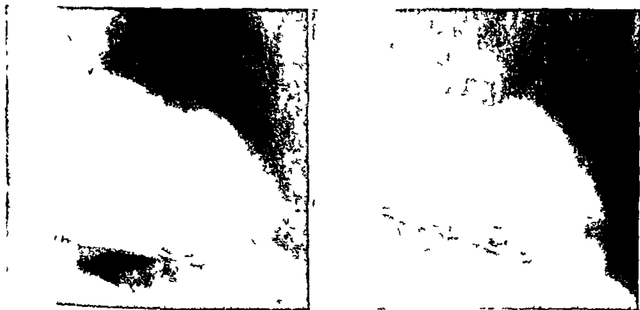


Fig 3 The left ventriculogram in the RAO projection is shown in diastole *(left)* and systole *(right)* Marked akinesis of the anterior wall apex and distal inferior wall is demonstrated with preservation of function in the proximal inferior wall.

sponded poorly to intravenous lidocaine and was exacerbated by oral quinidine Intravenous procainamide abolished the dysrhythmia and an oral preparation was substituted An electrophysiologic study to assess the degree of ventricular irritability was undertaken with the patient receiving procainamide and demonstrating therapeutic serum levels Four sites in the ventricle studied for the repetitive ventricular response during sinus rhythm and two sites studied during

allels that reported by Stern and associates[4] in which a young man in his 30s sustained an anterior myocardial infarction after an auto accident and at angiography was found to have complete occlusion of the proximal LAD with otherwise normal coronary arteries In both reports there were no apparent risk factors of coronary occlusion and no evidence of connective tissue disease

DR BLUMENTHAL The severity of chest wall trauma does not appear to correlate with the occurrence of coronary occlusion following trauma as was seen in our patient [3] An elastic compressible nonfracturing rib cage may result in more severe cardiac damage than one that fractures and dissipates mechanical energy [5, 24 …] Many of the cases [3, 8, 2] however were associated with local ecchymoses or rib fractures The most violent injury was an auto accident reported by Heyndrickx and colleagues[11] in which a patient suffered major trauma to the thoracic cage and sustained rupture of the right coronary artery

DR BERNADINE BULKLEY The etiology of myocardial infarction due to nonpenetrating chest injury is not entirely clear Studies in the previously reported cases suggest varied etiologies (1) atherosclerotic heart disease either diffuse or isolated complicated by hemorrhage into a plaque or spasm (2) coronary thrombosis due to direct vascular trauma (3) spasm in normal coronary arteries (4) frank rupture of the vessel (5) dissecting aneurysm and (6) coronary embolization The presence of coexisting coronary artery disease has been raised by some as a necessary predisposing factor In the 16 cases under analysis however only four had evidence of extensive atheromatous disease Another four were described as having slight or insignificant lesions Unfortunately in some of the earlier cases the degree of obstruction was not quantitated How important a role slight or insignificant lesions may have played in the subsequent myocardial infarctions remains a matter [illegible] speculation Of cases without other le[illegible]on [illegible] eight were documented by angiography Thu[illegible] in thi[illegible] small group of patients preexi[illegible] [illegible] tery disease was not a [illegible] [illegible] duction of coronary occlu[illegible] [illegible] [illegible]uma

Patients with [illegible] [illegible]ease however may be at a greate[illegible] [illegible] injury related to blunt trauma as con[illegible] [illegible] a person with normal coronary arteries when one considers that diseased and brittle vessels lying on the surface of the heart may be subjected to direct damage Levy[7] believed this to be the case with the 49 year old woman in whom he observed hemorrhage within the plaque and seepage of blood through the intimal lining with thrombus formation Moritz[3] stated in his review that plaques in atherosclerotic coronary arteries are often richly vascularized with newly formed thin walled capillaries that are inadequately supported by the surrounding liquid debris and suggested that such vascular plaques are subject to spontaneous or traumatically induced rupture into the lumen of the diseased artery

DR VLAY In a 25 year old woman however one would suspect that there is less likelihood of preexisting coronary disease Thrombus has been suspect in the pathogenesis of traumatic coronary artery occlusion Seven of the nine autopsied cases described thrombotic occlusion of the coronary vessel One may speculate that shearing forces during the traumatic episode may produce a small intimal tear which subsequently acquires platelets fibrin and other clotting system components until thrombosis is complete Spasm with subsequent thrombus formation also may occur in response to local injury although documentation of this is not available Such a mechanism was proposed after blunt trauma to the chest of laboratory animals [3] it was felt that localized blows transmitted to the precordium induced coronary spasm Gertz[11] has presented preliminary evidence that spasm results in endothelial damage using a feline model Spasm produced in the basilar as well as in the coronary arteries resulted in local damage and subsequent thrombosis

DR BLUMENTHAL The findings in some patients with myocardial infarction after trauma but with normal coronary arteries on angiography [illegible] has raised the question of whether the injury was ever to the coronary vessel but was rather a severe myocardial contusion Myocardial contusion has been easily produced experimentally [illegible] and is frequently identified by ECG elevated CK and other cardiac isoenzymes or demonstrated by extraction or lack of uptake by a variety of radionuclide tracers [illegible] Nevertheless the identification of normal coronary arteries at angiography weeks to months after the infarct

Angiogram	Autopsy	Atherosclerotic coronary artery disease	Between trauma & symptoms of MI
	Thrombotic occlusion of LAD with large infarct	Yes (extensive)	9 days
	Organized thrombus LCA recanalized Death due to RCA occlusion ten months after original infarct	Yes (extensive)	1 hour
	Occlusion by thrombus 1 cm from origin	Yes (slight)	Immediate
	Traumatic dissecting aneurysm of LAD	Yes (insignificant)	6 days
	Anteroseptal MI occlusion LAD by thrombus	Yes (extensive)	Immediate
	Occlusion of LAD at point of narrowing with hemorrhage into wall and small red fibrinous thrombus blocking lumen	Yes (extensive)	2 hours
	Large organizing thrombus in left circumflex	Yes (insignificant)	Immediate
Normal coronary arteries		No	10 hours
	Complete rupture of RCA cm from orifice covered with a small fresh thrombus	Yes (slight)	Immediate
Total obstruction in proximal LAD		No	Immediate
Complete occlusion left circumflex		No	[illegible] hour
Normal coronary arteries		No	Immediate
Total occlusion LAD 1 cm from origin		No	Immediate
Severely obstructed RCA 1 cm beyond its origin		No	Immediate
Total occlusion RCA 1 cm beyond its origin		No	Immediate
Total obstruction in proximal LAD	Proximal LAD obstructed by fibrous plaque with recanalization	No	5 days

did observe nine cases of complete rupture of a major coronary artery and a tenth involving an intimal tear Sporadic reports of myocardial infarction following blunt trauma and substantiated by autopsy or angiography have appeared in the medical literature over the past 40 years

Myocardial infarction after blunt chest trauma however as may have occurred in this young woman is rare We could identify only 15 prior reported cases with documentation by autopsy or angiogram and findings in these patients are summarized in Table I Approximately 25 other reports suggesting myocardial infarction following nonpenetrating chest injury were excluded from this review due to lack of angiographic or autopsy documentation The 16 patients summarized in Table I included 13 men and three women with a mean age of 38 years (range 10 to 62 years) Eight of the 16 had atherosclerotic coronary artery disease which was described as extensive in four of them The anterior descending branch of the left coronary artery (LAD) was involved in ten cases the left circumflex was involved in two cases and the right coronary was involved in four cases

The presently described case most closely par

transmural anteroseptal and apical transmural myocardial infarct Her coronary arteries had normal takeoff from the aorta and showed no evidence of dissection or aneurysm formation Her proximal left anterior descending coronary artery was totally occluded by a fibrous plaque compatible with atherosclerosis or with a previous thromboembolic event with subsequent organization (Fig 4) The remainder of her coronary arteries and her aorta were completely free of atherosclerotic plaque There was no evidence of recent infarction or coronary thrombosis to account for the terminal event

DR BLUMENTHAL Dr Bulkley how do you account for the delayed presentation of the infarction?

DR BULKLEY Most unclear and atypical in this young patient is the occurrence of the infarct five days after the blunt trauma Of the previously reported 15 cases only two others had evidence of delayed myocardial injury after the chest trauma one 6 and one 9 days after the traumatic event The ECGs and the pattern of serum creatine kinase elevation in our present patient support the clinical history suggesting that the infarct occurred five days after the trauma Initially the electrocardiogram revealed an acute infarct with ST T changes that evolved with loss of R waves in the precordium Although the precise etiology remains unknown, the precipitating event in this patient was assumed to be a coronary thrombosis and/or embolism Unfortunately morphologic findings five months after the event do not entirely resolve the question of etiology An organized thrombus or embolus may be indistinguishable from a fibrous atherosclerotic plaque of long standing duration Considering the patient s youth and absence of symptoms prior to the event it seems likely however that the high grade narrowing of her coronary artery by fibrous plaque seen at autopsy in the setting for otherwise normal coronary arteries may well have been related to a thrombotic occlusion Thus the histologic changes in her coronary artery are compatible with although not diagnostic of a prior thrombotic event The autopsy findings do provide evidence however that there was a coronary event related to the infarct and that the event was not a primary coronary dissection contusion or laceration Furthermore the autopsy findings show [illegible] rmality only in the left anterior descending coronary artery [illegible] this not the vessel most often involved by bl[illegible] chest trauma?

DR VLAY In ten of the 16 cases reported (63[illegible]) the vessel involved after blunt chest trauma causing myocardial infarction was the a[illegible] descending branch of the left coronary artery The anatomical location of this artery very likel[illegible] makes it particularly susceptible to the effects of trauma Noteworthy however is the predominance of involvement of this artery in cases of coronary artery embolization and dissection Explanations advanced for the predilection of the left coronary artery in these latter conditions of embolism have included (1) the larger caliber of the left coronary artery compared to the right and (2) the geometry of the left coronary arter[illegible] branches making the left anterior descendi[illegible] branch more liable to occlusion Arguments against a left predominance include the fact tha[illegible] (1) a right coronary embolus may not be fatal or may go unrecognized and that (2) right occlusion may be more distal with less loss of myocardial tissue With coronary artery dissection the left anterior descending coronary artery is again the most frequently involved usually within two centimeters of the aortic ostium but the reason for this predominance is unclear

DR BULKLEY Only certain types of trauma seem to lead to this unfortunate myocardial injury Not surprisingly automobile accide[illegible] were implicated in eight of 16 (50%) reported cases and many of the anecdotal accounts involve steering wheel trauma Such injuries might be prevented by wearing shoulder harness seat belts Assault with a fist was responsible for a[illegible] other three (19%) cases The other 31% were accounted for by sporting activities and industrial accidents In our patient steering wheel injury albeit mild appeared to be the culprit The findings in this patient and in several others reported sug[illegible] that traumatic coronary artery disease should [illegible] least be entertained in the patient with se[illegible]ere a[illegible] persistent chest pain after chest trauma even of [illegible] mild degree of severity Although at the prese[illegible] time there is little evidence that early interven[illegible] tion might alter the course of this event ea[illegible] recognition of an impending coronary occlu[illegible] in at least the few patients with delayed myocardial injury may offer the potential for reparative intervention

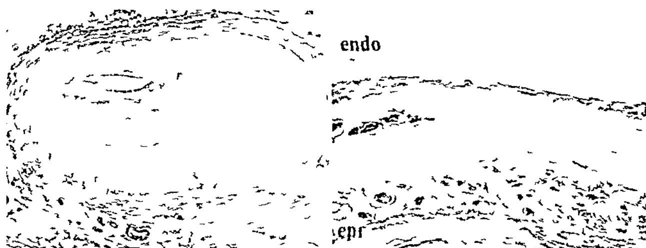


Fig 4 *Left* Histologic section from the proximal left coronary artery showing a near total occlusion by a fibrous plaque (Hematoxylin and eosin original magnification ×30) *Right* Histologic section through site of anterior wall infarction showing a transmural scar a thickened endocardium *(endo)* overlying the infarct and organized epicardial *(epi)* adhesions compatible with a focal pericarditis (Hematoxylin and eosin original magnification ×30)

not sufficient to rule out acute thrombotic ents as precipitating the acute infarct Also vere coronary spasm as the result of the trauma ight result in infarction but would show normal oronaries angiographically although spasm is ften noted at a site of coronary narrowing oronary artery embolus similarly cannot be xcluded The findings in our patient are clearly coronary event associated with an infarct in the bnormal vascular distribution rather than the esult of a contusion Another unusual cause of raumatic myocardial infarction also unlikely in ur patient is a frank rupture of a coronary rtery [1] In one patient in which it was eported [11] an acute infarct resulted from a com lete rupture of the right coronary artery asso iated with laceration of the pericardium and erniation of the heart the latter preventing ericardial tamponade and allowing brief surviv l

DR VLAY Dissection of a coronary artery may lso result from trauma [6] however dissection was dentified in only one of the 16 patients reported ne might suggest that a small intimal tear radually expanded over the course of six days nd then suddenly proceeded to dissection It is enerally believed however that coronary dissec ions have a rapidly fatal course and among atients dying of coronary dissection reported in he literature [14] trauma was an infrequently associated event A final mechanism that must be considered is coronary embolus secondary to mural thrombosis from an injured left ventricular myocardium Levy cites Randerrath s case of the 34 year old soccer player who was struck in the chest by a ball and collapsed with pallor and cold diaphoresis with death on the following day The autopsy revealed a recent small apical aneurysm with fresh mural thrombosis An embolus was identified in both the LAD and the RCA

In summary we have a 25 year old woman with flush occlusion of the anterior descending branch of the left coronary artery and infarction in its distribution who subsequently had a sud den death Due to the absence of other angio graphic lesions in her coronary tree the most likely etiology is thrombosis related to an injury to the artery or an embolic event The cause of death most probably was a ventricular arrhyth mia although infarction must not be excluded Dr Bulkley will now present the pathologic findings

Discussion of pathologic findings

DR BULKLEY At autopsy the only abnormali ties were present in the patient s heart and lungs Her lungs were heavy and showed evidence of diffuse pulmonary congestion and focal areas of intralveolar edema Her heart weighed 350 grams and had left ventricular dilatation and a large

Coronary artery embolism and myocardial infarction A clinicopathologic study of 55 patients Ann Intern Med 88 155 1978
47 Bulkley B and Roberts W C Dissecting aneurysm (hematoma) limited to coronary artery Am J Med 55 747 1973
48 Brody G L Burton J F Zawadzki E S and French A J Dissecting aneurysms of the coronary artery N Engl J Med 273 1 1965
49 Roy J J and Klein H Z Dissectin aneurysm of the coronary artery JAMA 218 104* 19 1
50 Wenger N K and Bauer S Coronary embolism Review of the literature and presentation of fifteen cases Am J Med 25 549 1958
51 Smith J C Dissecting aneurysms of the coronary arteries Arch Pathol 99 11 1975

REFERENCES

1 Greene H L Reid P R and Schaeffer A H The repetitive ventricular response A predictor of sudden death, N Engl J Med 299 ⁷⁹9 1978

2 Parmley L F Manion W C and Mattingly T W Nonpenetrating traumatic injury of the heart Circulation 18 3 1 1958

3 Warburg E Myocardial and pericardial lesions due to nonpenetrating injury Br Heart J 2 271 1940

4 MacDonald D Repeated and fatal coronary thrombo is in a young man J.A.M A 116 2846 1941

5 Jokl E and Greenstein J Fatal coronary sclerosis in a boy of ten years Lancet 2 659 1944

6 Hedinger C Contusio cordis mit Spatrupter der linken Herzkammer Cardiologia 12 46 1948

7 Levy H Traumatic coronary thrombosis with myocardial infarction Arch Intern Med 84 261 1949

8 Lehmus H J Sundquist A B and Giddings L W Coronary thrombosis with myocardial infarction secondary to nonpenetrating injury of the chest wall AM HEART J 47 470 1954

9 Stewart J S S Primary traumatic coronary thrombosis Br Med J 1 739 1967

10 Harthorne J W Kantrowitz P A Dinsmore R E and Sanders, C A Traumatic myocardial infarction Report of a case with normal coronary angiogram Ann Intern Med 66 341 1967

Hevndrickx G Vermeire P Goffin Y and Van den Bogaert P Rupture of the right coronary artery due to nonpenetrating chest trauma Chest 65 577 19 4

Stern T Wolf R Y Reichart B Harrington O B and Crosby G Coronary artery occlusion resulting from blunt trauma J A M.A. 230 1308 1974

Oren A Bar Shlomo B and Stern S Acute coronary occlusion following blunt injury to the chest in the absence of coronary atherosclerosis AM HEART J 92 501 1976

de Feyter P J and Roos J P Traumatic myocardial infarction with subsequent normal coronary arteriogram Eur J Cardiol 6 25 1977

Candell J Valle V Paya, J., Cortadellas J Esplugas E and Rius J Post traumatic coronary occlusion and early left ventricular aneurysm AM HEART J 97 509 1979

Oliva P B Hilgenberg A and McElroy D Obstruction of the proximal right coronary artery with acute inferior infarction due to blunt chest trauma Ann Intern Med 91 205 1979

Leinoff H D Acute coronary thrombosis in industry Arch Intern Med. 70 33 1942

Jones F L Transmural myocardial necrosis after nonpenetrating trauma Am J Cardiol 26 419 1970

Madoff I M and Desforges G Cardiac injuries due to nonpenetrating thoracic trauma Ann Thorac Surg 14 504 1972

Borodkin H D and Massey F C Myocardial trauma produced by nonpenetrating chest injury AM HEART J 53 95 1957

Relation of myocarditis and coronary thrombosis to trauma Queries and minor notes, J.A M A 101 1503 1933

Bean, W B Infarction of the heart A morphological and clinical appraisal of three hundred cases I Predisposing and precipitating conditions AM HEART J 14 684 1937

Kahn M H., and Kahn S Cardiovascular lesions following injury to the chest Ann Intern Med 2 1013 1929

24 Bright E F and Beck C S Nonpenetrating wounds of the heart AM HEART J 10 93 391 1934

25 Arenberg H Traumatic heart disease A clinical study of 250 cases of nonpenetrating chest injuries and their relation to cardiac disability Ann Intern Med 19 3 6 1943

26 Watson J H and Bartholomae W M Cardiac injury due to nonpenetrating chest trauma Ann Intern Med 52 8 1 1960

27 DeMuth W E Baue A E and Odem J A Contusions of the heart J Trauma 7 443 1967

28 Sigler I H Trauma of the heart due to nonpenetrating chest injuries J A M.A 119 855 1942

29 Barber H The effects of trauma direct and indirect on the heart Q J Med 13 137 1944

30 Moritz A R Trauma stress and coronary thrombosis J A M.A 156 1306 1954

31 Schlomka G Commotio cordis Klin Wchnschr 12 167 1933

32 Gertz S D Vascular damage and thrombosis from spasm N Engl J Med 300 197 1979

33 Sakurai H Lukban S Litwak R and Perevo J A Left ventricular aneurysm due to blunt trauma N Y State J Med 75 2367 1974

34 Kissane R W Fidler R S and Koons R A Electrocardiographic changes following external chest injury to dogs Ann Intern Med 11 90 1937

3 Potter R T Stefko P L Bertrand C A McNeill T M O Brien G F Garret R and Chamberlain J M Blunt cardiac trauma a pathophysiologic study Ann Thorac Surg 1 437 1965

36 Doty D B Anderson A E Rose E F Go R T Chiu C L and Ehrenhaft J L Cardiac trauma Clinical and experimental correlations of myocardial contusion Ann. Surg 180 452 1974

3 Utley J R Doty D B Collins J C., Spaw E H Wachtel C and Todd E P Cardiac output coronary flow ventricular fibrillation and survival following varying degrees of myocardial contusion J Surg Res 20 539 1976

38 Dolara A Pasla M and Pampaloni M Electrocardiographic findings in 98 consecutive nonpenetrating chest injuries, Dis Chest 52 50 1967

39 Tonkin A M Lester R Guthrow C E Roe C R Hackel, D B and Wagner G S Persistence of MB isoenzyme of creatine phosphokinase in the serum after iatrogenic chest trauma Circulation 51 627 1975

40 Lindsay D Manin T and Finlev P R Transient elevation of serum activity of MB isoenzyme of creatine phosphokinase in drivers involved in automobile accidents Chest 74 15 1978

41 Martin L G Larose J H Sybers R G., Tyras D H and Symbas P N Myocardial perfusion imaging with Tc albumin microsphere Radiology 107 367 19 3

42 Go R T Doty D B Chiu C L and Christie H A new method of diagnosing myocardial contusion in man by radionuclide imaging Radiology 116 107 1975

43 Maseri A L Abbate A Baroldi G Chierchia S Marzilli M., Ballerstra A M Severi, S Parodi, O Biagini, A., Distante A., and Pesola A Coronary vasospasm as a possible cause of myocardial infarction N Engl J Med 299 1271 1978

44 Prinzmetal M Kennamer R and Merliss R Angina pectoris I A variant form of angina pectoris Am J Med 27 375 1959

45 Hillis, L D and Braunwald E Coronary artery spasm N Engl J Med 299 695 1978

46 Prizel K. R., Hutchins G M and Bulkley B H

mal or absent and there is instead a predominant systolic dip (X descent)[3]

Paradoxical pulse is present as a rule in cardiac tamponade The principal exceptions are those instances in which it may be obscured by arrhythmia or by other complicating features In constrictive pericarditis on the other hand paradoxical pulse is usually of lesser degree than in tamponade and may be absent

Kussmaul s sign occurs in some patients with constrictive pericarditis although probably not the majority In cardiac tamponade however if strictly defined Kussmaul s sign occurs rarely at most perhaps never Reported instances of Kussmaul s sign in tamponade are numerous but none are substantiated by direct pressure records such reports probably result from failure to recognize associated constrictive pericarditis in some instances while in others an inspiratory increase in amplitude of venous pulsation may be mistaken for a true rise in central venous pressure Still other cases represent instances where the sign is elicited with an instructed deep inspiration to which the patient responds by performing Valsalva s maneuver The differences in special features are perhaps not so widely appreciated as they might be and the principal reason for this may be that there has been no readily understandable or generally accepted explanation for them Indeed the mechanisms of the special hemodynamic features themselves especially paradoxical pulse and Kussmaul s sign have not been adequately understood *An additional difficulty is that clini*cal assessment is not so accurate or quantitative as direct pressure records in assessing these signs Further the classification of patients is often difficult because the objective diagnosis of either cardiac tamponade or constrictive pericarditis requires a combination of clinical hemodynamic and anatomic pathological data which are often not available in the clinical setting

Objective diagnosis of tamponade and constriction

The objective diagnosis of cardiac tamponade defined as a condition in which there is compression of the heart by fluid in the pericardial space under increased pressure requires the measurement of an elevated level of intrapericardial pressure and of correspondingly elevated levels of pressure within the chambers of the heart in diastole A further requirement i the return of hemodynamic measurements to normal after removal of enough pericardial fluid to reduce the intrapericardial pressure to normal Constrictive pericarditis is best defined as a condition in which there is compression or restriction of the heart by the pericardium either by the visceral layer or by an adherent parietal layer with hemodynamic abnormalities including elevated levels of diastolic pressure in the cardiac chambers which return to normal after surgical removal of the pericardium

It is often difficult to meet these diagnostic criteria in clinical practice Patients who are suspected of having cardiac tamponade because of the presence of pericardial effusion and elevated levels of venous pressure may be shown by hemodynamic study to have instead one of several other conditions alone or in combination Some have right sided congestive heart failure due to valvular or myocardial disease with increased amounts of pericardial fluid which is not under increased pressure and represents simply one site of accumulation of excess extracellular fluid Others especially patients on chronic dialysis for renal failure have predominantly fluid overload and left ventricular failure with an associated pericarditis and pericardial effusion of lesser importance A few usually on the basis of neoplastic disease have superior vena caval obstruction rather than tamponade Finally some patients have a combination of tamponade and constriction due to pericardial *fluid under increased pressure* associated with constriction of the heart by the visceral pericardium (epicardium) this condition (effusive constrictive pericarditis) can only be demonstrated objectively by showing that the venous pressure level remains elevated with other features consistent with constriction after the intrapericardial pressure is reduced to normal by removal of fluid[3]

Observations in subacute constrictive pericarditis

Patients with effusive constrictive pericarditis usually have a subacute course measured in weeks or months rather than the period of years which is frequently seen in chronic constrictive pericarditis Hemodynamic studies in these patients have provided insight *into the* basis for the differing patterns of special hemodynamic features of tamponade and constriction In general they have features similar to those of tampon

Fundamentals of clinical cardiology

On the elastic and rigid forms of constrictive pericarditis*

E William Hancock M D
Stanford Calif

The effects of pericardial disease on the circulation result essentially from compression (restriction) of the heart making it more difficult for the heart to fill with blood during diastole The function of the heart during systole does not appear to be impaired in most cases The cardiovascular system typically achieves a compensation for compressive pericardial disease by increasing the central venous pressure to a level at which adequate filling of the heart in diastole can still occur despite the degree of restriction which the pericardial disease imposes Thus except in the most severe or the most rapidly developing cases where compensation is inadequate or in cases in which there are additional abnormalities of fluid balance or in the function of the heart or circulation the clinical and hemodynamic picture of compressive pericardial disease reflects essentially a sustained elevation of central venous pressure In this respect the two classical pericardial disorders cardiac tamponade (compression of the heart by pericardial fluid under increased pressure) and constrictive pericarditis (restriction of the heart by a thickened and adherent pericardium) are identical

Special hemodynamic features of pericardial disease

In compressive pericardial disease there are in addition to the elevated level of venous pressure four principal hemodynamic features which although not unique to pericardial disease are somewhat distinctive and are helpful in the clinical differentiation of pericardial disease from other disorders which may also cause elevated levels of venous pressure These features are (1) the occurrence of nearly equal levels of pressure in all chambers of the heart during diastole (2) the pattern of an early diastolic dip and later diastolic plateau in the ventricular pressure waveform and the corresponding prominent early diastolic dip in the atrial pressure waveform (3) the exaggerated variation in systemic arterial pressure with respiration (paradoxical pulse) and (4) the rise in venous pressure with inspiration (Kussmaul's sign)

Equilibration of intracardiac pressure levels in all cardiac chambers in diastole is a feature common to cardiac tamponade and constrictive pericarditis since both forms of pericardial disease typically produce compression which is symmetrical around the entire heart However the dip plateau waveform the paradoxical pulse and Kussmaul's sign are known to occur in somewhat different patterns in cardiac tamponade than in constrictive pericarditis

Hemodynamic differences between tamponade and constriction

The dip plateau pattern in the ventricular pressure waveform is a typical feature in constrictive pericarditis. In cardiac tamponade on the other hand there is little or no early diastolic dip pressure in the ventricle falls only partially during the early relaxation phase of the cardiac cycle and the plateau of elevated diastolic pressure is present from the beginning of diastole Correspondingly the prominent early diastolic dip (Y descent) is a feature of the venous pressure waveform in constrictive pericarditis but not in cardiac tamponade where the Y descent is mini

From the Cardiology Division, Stanford University School of Medicine Stanford, Calif

Received for publication Jan. 4 1980

Reprint requests E. William Hancock, M D Cardiology Division Stanford University Medical School, Stanford CA 94305

*Presented at the Fifteenth Lawrence B Ellis Lecture Harvard Medical School, Oct 29 1979

000- 8 03 80/1-091- + 0 $00 70/0 © 1980 The C V Mosby Co

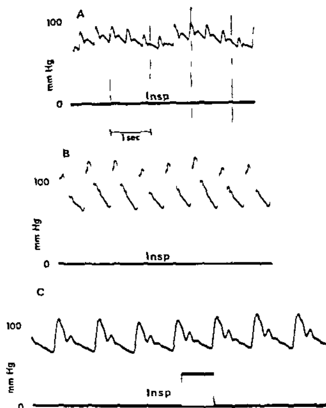


Fig 2 Varying degrees of paradoxical pulse are seen in direct pressure recordings from the aorta in patients with three types of compressive pericardial disease The three patients are the same as those illustrated in *Fig 1* At the top (*A*) in cardiac tamponade respiratory variation in arterial pressure is exaggerated a typical paradoxical pulse In the middle (*B*) in subacute constrictive pericarditis the respiratory variation is less but still slightly exaggerated for quiet respiration At the bottom (*C*) in chronic calcific constrictive pericarditis only an instructed deep inspiration is followed by an appreciable fall in pressure none could be appreciated during quiet uninstructed breathing The instructed deep inspiration is indicated by *Insp*

cle which is analogous to a rigid shell surrounding the heart At the beginning of diastole when the heart is least full it is comfortably smaller than the volume of the shell and is not constricted Thus as the ventricular myocardium relaxes the pressure in the ventricle falls rapidly to a minimum level near zero The combination of the high venous pressure and the unrestricted heart results in a rapid rate of blood flow into the ventricle in early diastole As the ventricle enlarges it reaches the fixed volume of the shell and from this time through the remainder of diastole the heart is severely restricted Any further filling during the restricted phase of diastole would be accompanied by a steep rise in pressure in the ventricle In such cases virtually all of the filling takes place in early diastole restriction comes into play abruptly and the plateau of the pressure recording represents a phase in which little or no further filling takes place

In cardiac tamponade the heart is compressed throughout the cardiac cycle This may be inferred from the pressure recording in the pericardial space which shows an elevated pressure level throughout the cycle The smaller size of the heart in systole does result in some decompression but the degree of compression is more constant and less dependent on the size of the heart than it is with the rigid shell type of constriction With tamponade therefore, the heart is compressed from the beginning of diastole The pressure in the ventricle does not fall to a normal level near zero, in early diastole but falls only to a level slightly above the pressure level in the pericardial fluid Filling of the ventricle is impeded in early diastole nearly as much as in later diastole flow into the ventricle takes place throughout diastole and the pressure waveform shows no early diastolic dip

The lesser prominence of the dip plateau waveform in patients with effusive constrictive pericarditis can be explained as the result of a degree of associated tamponade in such cases. Its similar lack of prominence in some patients with subacute constrictive pericarditis, even in the absence of an element of tamponade or of any pericardial effusion at all suggests another explanation Rather than a rigid shell with a fixed volume the patients with subacute constriction may be considered to have a fibroelastic type of constriction analogous to elastic rubber band wrapped around the heart Such an elastic constriction would compress the heart continuously throughout the cardiac cycle in the same manner as a tense pericardial effusion Thus the pattern of impedance to filling and the ventricular pressure waveform in subacute fibroelastic constrictive pericarditis with or without effusion might be expected to resemble that of cardiac tamponade as much or more than it would resemble that of a chronic rigid shell type of constrictive pericarditis

Mechanism and significance of the venous pressure waveform

The diastolic portion of the central venous pressure waveform reflects directly the pressure

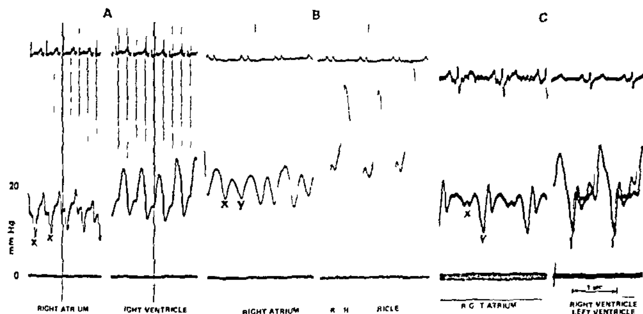


Fig 1 Contrasting waveforms are seen in pressure recor[illegible] the ri[illegible]t atrium and ri[illegible]ht ventricle in patients with three types of compressive pericardial disease On [illegible] in a 1[illegible] year old woman with cardiac tamponade due to leukemia the ventricular waveform [illegible] early and late diastolic pressure level and an inconspicuous dip plateau pattern while the atrial wav[illegible] prominent systolic (X) descent and absence of the early diastolic (Y) descent In the middle (B) in a [illegible] an with idiopathic subacute constrictive pericarditis without effusion the ventricular pressure [illegible] prominent dip-plateau pattern the atrial *pressure waveform shows approximately equal X and Y de[illegible] M or W contour On the right (C)* in a 49 year-old man with idiopathic chronic calcific [illegible] the ventricular pressure waveform shows a prominent dip plateau pattern the atrial pressure [illegible] shows a predominant early diastolic descent (xY pattern) All records are at the same paper speed and [illegible]

de even though their disease process and its management is essentially that of constriction The dip plateau in the ventricular pressure wave form is present but the dip is not so deep not approaching the zero level as it is in classical chronic constrictive pericarditis The venous pressure waveform usually shows a predominant systolic dip with a lesser but still present early diastolic dip (Xy) or a form with approximately equally prominent systolic and diastolic descents (XY) After removal of the fluid when only the constrictive element remains the early diastolic dip becomes more prominent in both the ventricular and the atrial pressure waveforms

Paradoxical pulse is consistently present in effusive constrictive pericarditis resembling cardiac tamponade in this respect It is relatively little affected by removal of the fluid Kussmaul s sign may occur in effusive-constrictive cases but is probably less frequent than in chronic constrictive disease Patients with subacute noncalcific constrictive pericarditis even in the absence of effusion also tend to show patterns of the special hemodynamic features which are intermediate between those of tamponade and classical constriction In this regard Wood contrasted active and inactive cases of tuberculous pericarditis while Kesteloot and Denef emphasized the special features of subacute constrictive epicarditis

Thus the differing hemodynamic features in acute cardiac tamponade and chronic constrictive pericarditis represent the two extremes of a spectrum of cases In the middle are patients with subacute constriction often associated with various degrees of pericardial effusion who show intermediate patterns of the special hemodynamic features Figs 1 and 2 illustrate the spectrum of atrial and ventricular pressure waveforms and of the paradoxical pulse

Mechanism and significance of the dip plateau waveform

The dip plateau waveform of the ventricular pressure recording in constrictive pericarditis is best understood as resulting from a type of mechanical impedance to the filling of the ventri

Table I Comparison of the frequency and relative prominence of several clinical and hemodynamic features in three types of compressive pericardial disease

	Tamponade	*Subacute (fibroelastic) constriction*	*Chronic (rigid shell) constriction*
Pericardial effusion	present	often present	absent
Pericardial calcification	absent	usually absent	often present
Abnormal P waves or atrial fibrillation	absent	usually absent	often present
Dip-plateau pattern	inconspicuous	moderately prominent	prominent
Venous waveform	X or Xy	Xy or XY	XY or xY
Paradoxical pulse	prominent	moderately prominent	inconspicuous
Kussmaul s sign	absent	usually absent	occasionally present
Early diastolic sound	absent	usually absent	often present

The early diastolic sound of constrictive pericarditis

The early diastolic sound (pericardial knock) of constrictive pericarditis is related to the dip plateau pressure waveform in the ventricle occurring near the end of the rapid filling phase in early diastole [1] The sound is present frequently in chronic constrictive pericarditis infrequently in subacute constrictive pericarditis and rarely if ever in cardiac tamponade These differences are understandable in terms of the differing prominence of the dip plateau pattern in these conditions The early diastolic sound may therefore be considered a sign of the rigid shell type of constrictive pericarditis

Clinical implications

The clinical picture of constrictive pericarditis has changed in recent years Tuberculosis is a less frequent cause than in the past and the chronic calcific type of disease often due to tuberculosis in the past is now less frequent than the subacute noncalcific form The majority of cases of constrictive pericarditis today are idiopathic (including those thought to follow viral infection) while smaller numbers occur after radiation rheumatoid arthritis bacterial and fungal infections chronic hemodialysis cardiac surgery and other conditions Constrictive pericarditis occurring in these latter conditions is in general likely to be recognized in the acute or subacute stage Thus the features described here as being characteristic of subacute fibroelastic constriction are found in many of the patients who are seen now with an initial presentation of constrictive pericarditis

The clinical similarity of fibroelastic constriction to cardiac tamponade and frequent association with pericardial effusion makes the differential diagnosis between constriction tamponade a difficult one in many instances The distinction is a vital one because the cho between pericardiocentesis pericardiostomy pa rietal pericardiectomy or visceral pericardial stripping as well as the evaluation of the resul of any of these forms of treatment depend accurate assessment of the nature of the c sive process Measurements of intracardiac and intrapericardial pressures before and removal of pericardial fluid are more a than is clinical assessment in answering th questions Study of the pressure waveforms well as the levels of pressure is important Table I summarizes the distinguishing points

Finally the differentiation of elastic and types of compressive pericardial disease may be useful step toward understanding the mechanism of paradoxical pulse and Kussmaul s sign tions which have been so interesting to c and physiologists for so long but which have been so difficult to answer clearly

Summary

This article discusses a thesis regarding the pathophysiology of constrictive pericarditis thesis is that there are two forms of constrictio one being elastic and the other more analogou a rigid shell The two forms of constriction considered to cause different patterns of diagnostic signs of constriction The elastic is similar to cardiac tamponade and is assoc with prominent paradoxical pulse and syste descent in the venous pressure waveform. T rigid shell type has less prominent paradoxical pulse and a more conspicuous diastolic descent

waveform in the corresponding ventricle because these chambers are in unimpeded communication in diastole. The prominent early diastolic dip in the venous pulse in constrictive pericarditis thus reflects the brief period of unimpeded blood flow into the ventricle in early diastole. Its absence in cardiac tamponade reflects the presence of compression of the heart early in diastole as well as throughout the rest of the cardiac cycle and thus the absence of a conspicuous phase of rapid filling in early diastole. Patients with subacute fibroelastic constriction are likely to show intermediate degrees of prominence of the early diastolic dip.

The systolic portion of the venous pressure waveform is influenced by several factors. There is a fall in pressure related to the descent of the ventricles due to ventricular contraction. A fall in pressure is also related to relaxation of the atria in systole following contraction of the atria just before ventricular systole. Patients with constrictive pericarditis usually show a normal systolic (X) descent if they have sinus rhythm and the venous pressure shows an XY waveform (resembling a W or M). Those with atrial fibrillation lose much of the systolic descent and usually show an xY waveform.

In cardiac tamponade there is a special circumstance owing to the phasic change in pressure in the intrapericardial space. Intrapericardial pressure falls in systole because of the degree of decompression resulting from the smaller size of the heart. Right atrial pressure falls correspondingly in systole, the two waveforms are often closely parallel throughout the cardiac cycle, indicating their interdependence. Thus an X or Xy is the characteristic venous pressure waveform in tamponade.

Mechanism and significance of paradoxical pulse

Paradoxical pulse occurs by various mechanisms and in a variety of conditions other than compressive pericardial disease. The mechanism by which it occurs in pericardial disease has not been adequately understood. A variety of plausible theories have been offered and it appears that various factors may play a role. It has been accepted, however, since the experimental studies of Shabetai and associates, supported more recently by echocardiographic studies, that paradoxical pulse in cardiac tamponade is associated with a normal or even exaggerated increase in venous return to the right side of the heart during inspiration. There is a simultaneous decrease in filling of the left side of the heart with inspiration. The increase in venous return appears indeed to be a necessary part of the mechanism of paradoxical pulse in pericardial disease.

Occurrence of the increases in volume of the right heart chambers with inspiration depends on the transmission of the inspiratory fall in intrathoracic pressure to the interior of the heart. In cardiac tamponade this transmission occurs in a normal manner, probably because the pericardium is flexible and the pressure changes are well transmitted through the fluid. In constrictive pericarditis, on the other hand, the increase in venous return with inspiration may not occur to the normal degree because the pericardium takes the form of a rigid shell and the intrathoracic pressure variations are not transmitted to the interior of the heart. Thus the absence of paradoxical pulse in constrictive pericarditis may reflect loss of the normal inspiratory augmentation of venous return.

Patients with subacute fibroelastic constrictive pericarditis might be expected to transmit intrathoracic pressure variations to the interior of the heart more faithfully than the chronic cases who have a constrictive disease that is more analogous to a rigid shell. Paradoxical pulse would therefore be expected to be more conspicuous in the subacute cases.

Mechanism and significance of Kussmaul's sign

Kussmaul's sign may also be considered a sign of failure of transmission of intrathoracic pressure variations to the interior of the heart. The lowered intrathoracic pressure with inspiration draws more venous return to the intrathoracic venae cavae and right atrium, but in the presence of the rigid shell type of pericardial disease there is no associated decrease in the compression of the heart, and the increased right atrial filling is manifested as a rise in right atrial and central venous pressure. Thus Kussmaul's sign would not be expected in cardiac tamponade; it might occur in some instances of fibroelastic constriction but would be expected frequently only in the chronic rigid shell type of constrictive pericarditis.

Appraisal and reappraisal of cardiac therapy

Edited by Arthur C DeGraff and Julian Frieden

Diet in the treatment of hyperlipidemia

Norton Spritz M D
New York N Y

The possibility that alteration in diet may affect the risk for coronary artery disease is based on several observations First it is generally true that the diet of those nations with higher prevalence of atherosclerotic disease differs in several respects from that consumed in nations of low risk for this group of diseases[1] The first contains more total fat more saturated fat more cholesterol and total calories Second within populations with high prevalence for vascular disease the risk among individuals for clinical disease relates to their individual levels of plasma lipids and dietary alterations produce lowering of these levels toward apparently more favorable levels On the basis of these facts it would seem likely that both for populations as a whole and for individual patients changes in diet from their present high fat high calorie high cholesterol high saturated fat diet would be advantageous and should be expected to lessen the high rate of coronary vascular and other atherosclerotic diseases seen in American and other high risk populations For reasons that will be discussed below however an unequivocal demonstration that such changes are of advantage has not been achieved and several lines of evidence raise doubts about the efficacy of such changes for the population and have made uncertain the criteria for selection of individual patients in whom such diets should be prescribed

In contrast to the association between diet and vascular diseases seen when populations are compared to one another the role of diet as a factor for either the level of plasma lipids or the risk for vascular disease for individuals within a given population has not been established With t exception of the Tarahumara Indians who ha very low plasma and dietary cholesterol[2] carried out in Hawaii[4] Michigan[5] Framingham Massachusetts[6] as well as in Israel and Grea Britain[8] have failed to show a relationshi between prior diet and the risk of vascular di — for individuals within this wide range of popula tion groups While inability to demonstrate relationship between diet and disease or value for plasma lipids may relate to problems i assessing diet histories methodologic problems in plasma cholesterol measurement or the fact i plasma cholesterol and/or coronary heart dis are determined by a variety of variables of whi diet is only one these studies do not provide i themselves evidence that risk of coronary arter disease or cholesterol concentration within population is determined in an important way b diet

Similarly studies in which diet has been altered experimentally in man to determine the effect o such alterations on the risk of coronary arter disease have been equivocal While these and other dietary intervention studies ha shown that lipids can be lowered under situations it has been difficult to demonstrat that the lipid lowering has an effect on mortality In studies carried out in Los Angeles Norway[1] involving approximately 1 000 men f l lowed for eight and 11 years plasma cholesterol was lowered in the group given a low fat low cholesterol high polyunsaturated fat die by about 15% compared to controls and there wa an apparent decrease in the numbers of c coronary events Yet in neither study at a time was mortality lower in the diet gro compared to the controls This lack of effect c mortality is similar to the findings in seven studies in which plasma lipids were lowered b drugs

From the Med cal Serv   an Administration Medi cal Center and the Sch   N w Y rk Uni ersity

Received for publication

Reprint requests Norto   M D   Medical Service N w York VA Medical Cent   New York N Y 10010

0002 8 03/80/1209-4 + 01$00 40/0 © 1980 The C V M

the venous pressure waveform often associated with an early diastolic sound (pericardial knock) Recognition of these two types of constriction may be helpful in clinical diagnosis and in understanding the pathophysiology of pericardial disease

REFERENCES

1 Shabetai, R Mangiardi L. Bhargava V Ross J Jr and Higgins C B The pericardium and cardiac function Prog Cardiovasc Dis. 22 107 1979
2. Lange R L Botticelli J T Tsagiris T J Walker J A., Gani, M and Bustamante R A Diagnostic signs in compressive cardiac disorders Circulation 33 763 1966
3. DeCristofaro D and Liu C K The hemodynamics of cardiac tamponade and blood volume overload in dogs Cardiovasc Res 3 292 1969
4 Krikorian J G and Hancock, E W Pericardiocentesis, Am J Med. 65 808 1978
5 Hancock E W Subacute effusive constrictive pericarditis Circulation 43 183 1971
6 Wood P Chronic constrictive pericarditis Am. J Cardiol 7 48 1961
7 Kesteloot H and Denef B Value of reference tracings in diagnosis and assessment of constrictive epi and pericarditis Br Heart J 32 675 1970
8 Shabetai R Fowler N O Fenton J C., and Masangkay M Pulsus paradoxus J Clin Invest 44 1882 1965
9 Shabetai R Fowler N O and Guntheroth W G The hemodynamics of cardiac tamponade and constrictive pericarditis Am J Cardiol 26 480 1970
10 D'Cruz I A Cohen H C Prabhu R., and Glick, G Diagnosis of cardiac tamponade by echocardiography Changes in mitral valve motion and ventricular dimensions with special reference to paradoxical pulse Circulation 52 460 1975
11 Lange P A Tyberg T I., and Goodyer A V Pathophysiological genesis of a pericardial knock in constrictive pericarditis Circulation 59 and 60(Suppl II) II 9 1979

is not clear however whether a subset of the population either with normal or high plasma levels is more sensitive to cholesterol intake The major source of cholesterol in our diets is eggs and each egg contains about 200 mg of cholesterol thus a diet restricted in cholesterol below 300 mg a day greatly limits the number of eggs that can be consumed

The amount and nature of the dietery fat also affects plasma cholesterol levels It is well established that the cholesterol level (LDL cholesterol) is higher during the ingestion of fats comprised of saturated fatty acids than during the ingestion of polyunsaturated fats Fats such as olive oil made up of monounsaturated fats have little effect on cholesterol levels In general saturated fats are of animal origin such as those present in beef and pork meats and in dairy products that contain fats such as butter and cream Polyunsaturated fats are found in vegetable oils such as corn and safflower oils and in general the fats found in fish and fowl are more polyunsaturated than those of pork or beef While it is also generally true that foods rich in saturated fats contain more cholesterol saturation has an effect on cholesterol level independent of that due to cholesterol intake In most instances the cholesterol elevating effects of diet reflect the combination of an intake high in cholesterol as well as in saturated fat The sum of these effects is a variation of plasma cholesterol of 8% to 15% A decrease in total intake regardless of its composition that leads to weight loss produces an additional beneficial effect

HDL or high density lipoproteins HDL or alpha lipoproteins consist primarily of cholesterol and phospholipid and are composed of 50% protein In normal persons the HDL cholesterol is about one third of the total serum cholesterol and averages 55 mg /deciliter in women and 45 mg /deciliter in men Considerable evidence now indicates that in contrast to LDL the level of HDL relates in an inverse way to the risk of coronary artery disease Except for a well established increase in HDL with weight reduction the effect of diet on this type of lipoprotein remains uncertain Several reports suggest that increased intake [illegible] polyunsaturated fats lower HDL [illegible] as LDL cholesterol and a recent [illegible] investigation also found a positive rel[illegible] between cholesterol intake and HDL levels [illegible] findings require further confirmation and the magnitude of the potentially negative effects of diet if any is yet to be established

General considerations in the diet therapy of hyperlipidemia

1 Management aimed at altering elevat[ed] lipid concentrations should be a part of a gener[al] program for reduction of risk factors for cardi[o]vascular disease The two elements of this pro[]gram for which evidence is most secure are th[e] cessation or decrease in cigarette smoking and th[e] recognition and management of hypertensi[on] Several studies indicate that exercise will al[so] decrease the risk for cardiovascular events Th[e] use of diet or drugs to alter plasma lipids t[o] decrease the risk of vascular disease is a reaso[n]able component of therapy in patients with spe[]cial risk due to elevation in plasma lipids but th[e] efficacy of such therapy is less well establishe[d] than that for the other modalities discusse[d] above

2 Studies of the effect of diet on mortalit[y] have been disappointing but have been largel[y] limited to patients with or without heart disea[se] who are beyond the middle age These findings and the pathological evidence concerning th[e] time course of atherosclerotic disease sugge[st] that if diet is of value in prevention of this dise[ase] it will have to be instituted early in life There i[s] no real basis for the institution of diet therapy f[or] abnormal plasma lipids or in general for th[e] prevention of atherosclerosis in patients ol[der] than 65 years

3 Diet therapy should generally be determi[ned] by the nature of the pattern of abnormal i[n] plasma lipid concentration In evaluating [a] patient with hyperlipidemia total plasma chole[s]terol plasma triglyceride and HDL cholester[ol] should each be measured These values should b[e] obtained in patients who are following the[ir] normal patterns of activity and food intake a[nd] who have not recently suffered a serious illne[ss] such as a myocardial infarction Although th[e] cholesterol values are not altered immediately b[y] meals triglycerides are therefore plasma lipi[ds] should be determined at least 10 hours after th[e] last ingestion of fat

Although our understanding of hyperlipide[]mias is based on the concept of transport of li[pids] as lipoproteins lipoprotein eletrophoresis ran[] helpful in evaluation and treatment

Dietary factors and lipoproteins

It is now clear that an understanding of the relationship between plasma lipids the risk of vascular disease and attempts to alter this risk of diet requires consideration of these lipids as components of circulating lipoproteins There are four lipoproteins that occur in the plasma of normal persons and elevations in their levels reflects in almost all instances an increase in these lipoproteins rather than the presence of abnormal forms These lipoproteins are affected differently by dietary manipulations and have different statistical relationships to the risk for vascular disease In most instances with the exception of high density lipoproteins (HDL) measurement of cholesterol and triglyceride will suffice and the lipoprotein pattern can be predicted from those values making direct measurement of lipoproteins unnecessary

Chylomicrons Chylomicrons are lipoproteins made up almost entirely of triglyceride and they relate directly to fat ingestion in that they are produced by the intestine during fat absorption and do not appear normally in plasma except during the six to ten hours following fat intake Increase in plasma chylomicrons in the fasting state are not an important component of hyperlipidemias in man and in rare instances in which their concentration is increased they seem to have a weak association if any with increased risk for vascular disease For that reason they will not be discussed further except to make the general statement that they are reduced in plasma when fat intake is curtailed

VLDL or pre beta lipoproteins The lipoprotein other than chylomicrons that are rich in triglyceride is the VLDL or pre beta lipoprotein This lipoprotein is present at elevated levels in almost all adult patients with hypertriglyceridemia The amount of this lipoprotein in plasma has a direct relation to the risk of vascular disease It is increased in many patients with obesity particularly with high insulin concentrations and it is also seen at elevated levels in many diabetic patients of the insulin independent or maturity onset" type It has repeatedly been shown that weight reduction regardless of the composition of the diet results in most subjects in a decrease in plasma triglyceride (as VLDL) as well as in the accompanying hyperinsulinemia The long term effects of weight reduction with or without accompanying fall in plasma triglyceride upon the risk of developing cardiovascular disease remains unproven

In the patient with hypertriglyceridemia (elevated VLDL) who is not obese or in the patient who has achieved maximal weight loss but who remains hypertriglyceridemic the effect of diet is considerably less certain When normal persons or patients with hypertriglyceridemia are given a diet restricted in fat with a high carbohydrate content elevation in triglyceride occurs at least transiently Many authors believe that this response is temporary and that this diet coupled with cholesterol restriction and restriction of saturated fat is optimal therapy in patients with elevation of plasma triglyceride and in whom weight loss has been unsuccessful Other authors however have found that fat restricted high carbohydrate diets with total caloric content sufficient to maintain weight lead to increase in triglyceride concentration particularly postprandially In practice however this problem is rarely encountered since diet modified to restrict fat usually results in a decrease in total calories which in itself has a favorable effect on triglyceride concentration

Beta lipoproteins or LDL This lipoprotein consists mainly of cholesterol and most plasma cholesterol circulates in this form The well established direct association between plasma cholesterol concentration and the risk of vascular disease reflects variations in this lipoprotein Most of the variation in the plasma cholesterol within the normal population results from variations in the amount of this lipoprotein and in almost all instances elevations of cholesterol to abnormal levels in the absence of hypertriglyceridemia reflect increased levels of beta lipoprotein

It is now clear that in man alterations in cholesterol intake without other changes in diet affect its plasma level There is however uncertainty about the magnitude of this effect and the level of cholesterol intake beyond which such an affect can no longer be seen The average intake of cholesterol in the United States is 500 to 600 mg per day and it seems likely that increases beyond that range may have a small impact if any on the plasma level [2] In fact the major effect of dietary cholesterol seems to be demonstrable only when cholesterol intake is in the range of 300 mg per day and below and at that range restrictions in intake seem to produce decreases in plasma levels of about 10% to 15% It

Annotations

The importance of the history in the medical clinic and the cost of unnecessary tests

The use of routine investigations in the medical outpatient department is widespread The experienced doctor however realizes the limited value of such investigations and the importance of the clinical history and less so of the clinical examination in the diagnosis and management of patients To try to measure the usefulness of the three basic clinical methods—history examination and investigation—a two year study of medical outpatients was undertaken in a typical district general hospital serving a largely urban population of 225 000 people

All new patients referred by a family physician to a general medical clinic with a cardiological bias were included in the study The new patient was examined at his first attendance by the medical registrar or senior house officer who took a detailed history Routine investigations in all patients comprised hemoglobin white cell count erythrocyte sedimentation rate blood urea serum electrolytes and blood sugar estimations chest radiograph and electrocardiogram In addition any appropriate special investigations were also arranged such as exercise tests, barium studies, electroencephalography etc After a short interval the patient returned to the clinic to see me when the following steps were undertaken

1 The referral letter was read carefully and a note was made on whether a specific diagnosis was offered or whether referral was on the basis of symptoms/signs only

2 The history obtained at the first attendance was read and supplemented by any relevant questions that had been omitted by the junior staff

3 A specific diagnosis was made where possible and the management was decided on the basis of this completed history Management could be referral back to the family physician with or without treatment follow up in the medical clinic again with or without treatment, hospital admission or referral to another hospital department.

4 The initial examination findings were studied and any omissions again were made good by me

5 The diagnosis and management based on the history were reviewed in the light of the examination findings and any necessary modifications were made

6 Finally the investigations were assessed and any contribution by routine investigation or special investigation to diagnosis and management was assessed

To check the accura y of the hospital diagnosis a questionnaire wa circulated t famil physicians 18 to 30 months after the initial ref rral a kin whether the diagnosis was still considered correct or wheth r an ne developments had occurred to alter the hospita diagrosis. Th questionnaire was not however sent in relation to all patients seen Where the hospital diagnosi confirmed the ph ician s diagnosis—for instance in anginal patients—or where objective findings placed the dia nosi beyond doul t a in hyperten ion rheumatic heart disease diabetes thyrotoxicosis, etc no fol was considered necessary

In the two year period 630 outpatients were seen. The ro of the history examination and investigations in diagnosis is shown in Table I The history decided diagnoses in two thirds of the cardiovascular pa clinical examination contributed to only one-quarter of noses

When the 180 patients with chest pain are separately the history gave the diagnosis in 90% and nation was of no diagnostic value at all. Routine inves- tions mainly chest radiographs and electrocardiogr helped with only 3% of diagnosis and special tests, exercise electrocardiography helped with 6% T value of the history was also high in neurological with examination contributing even less than i lar problems and routine investigations were agair value

The history was also the main diagnostic method ratory urinary and miscellaneous problems. It was of value in alimentary problems, where the main diagnostic was provided by the special radiological tests. Special inve- gations were also of primary diagnostic value in en problems Clinical examination and routine were of no help in alimentary problems and little urinary problems

The importance of the history examination and tions in deciding management is shown in Table II history was the major determining factor in the lar neurological respiratory and miscellaneous Examination was most helpful in respiratory disease in diagnosing chronic bronchitis and emphysema, and less so in cardiovascular problems, where the main were hypertension and rheumatic heart disease Examina helped least in alimentary problems. Routine inves were of least value in cardiovascular and neurological agement and of most value in endocrine problems, mainly to blood sugar concentrations in diabetic pa also the routine chest radiograph was important in management of respiratory problems, and routine urine exa ination was helpful in urinary problems. The special in gations were again of most value in alimentary and problems

The incidence of abnormal results in all the routine gations is shown in Table III which also indicates whether t abnormality relates to the primary condition for which t patient was referred or to an associated unexpected clinically significant condition The limited number of po results with every investigation in every group of pa obvious. The over all incidence of positive blood or results did not exceed 5% and when considered in rela the primary condition for which the patient was referred.

0002-8703/80/1209 9 + 01$00 40/0 © 1980 The C V Mosb C

4 In patients with hypertriglyceridemia with or without moderate elevations of cholesterol the most important diet therapy is weight loss The patient should be made aware that the basis for a weight reduction program has specific therapeutic implications and that even moderate degrees of weight loss may be associated with decrease of plasma triglycerides towards normal levels even if optimal weight is not achieved

5 In patients with hypercholesterolemia in the absence of hypertriglyceridemia the diet should include the three elements of diet known to lead to cholesterol reduction—restriction of saturated fat provision of at least 10% of fat calories as polyunsaturated fats as well as a decrease in cholesterol intake In general terms this is a diet that restricts egg intake the ingestion of beef and pork products (including fat containing dairy products) and requires the addition of unsaturated fats in the form of vegetable oils and soft margarines In addition to eggs organ meats *such as liver kidney are also very* high in cholesterol content The most favorable sources of protein are fish and fowl In general shell fish such as lobsters and shrimp contain as much cholesterol per gram of protein as do beef and pork products The value of total fat restriction in a cholesterol lowering diet is not fully established Since there are marked individual variations in the response to this type of diet it is important to measure the effectiveness of the diet program after approximately four weeks of treatment In patients with serious elevations of their cholesterol concentrations in whom such therapy is ineffective therapy with drugs should be instituted.

6 Alcohol ingestion has a complex relationship to plasma lipid and development of atherosclerosis. In general *high levels of alcohol ingestion* seem to be associated with increase in VLDL triglyceride particularly in persons whose levels are already elevated There is little if any effect on LDL, but an increase in HDL cholesterol has been shown Thus alcohol could be advantageous or disadvantageous although most studies show that when ingested at more than moderate rates alcohol is associated with increases in mortality rates. The relationships between alcohol and coronary heart disease and its individual risk factors are discussed in a recent review

REFERENCES

1 M Gill S C Jr The relation of dietary cholesterol to serum cholesterol concentrations and to atherosclerosis in man Am J Clin Nutr 32 2 61 19 9

2 Clue C J Dietary fat and atherosclerosis Am J Clin Nutr 32 13 19 9

3 Carter Cerqueira M T Connor R W Wallace R B Malinow M R and Casdorph H R The plasma lipid lipoprotein and diet of the Tarahumara Indian of Mexico Am J Clin Nutr 31 1131 1978

4 Yano K Rhoad C C Kagen A and Tillotson J Dietary intake and the risk of the coronary heart disease in Japanese men living in Hawaii Am J Clin Nutr 31 1 0 19 8

Nichols A B Ravenscroft C Lamphiear D F and Ostrander L D Daily nutritional intake and serum lipid levels Tecumseh study Am J Clin Nutr 29 1384 19

6 The Framingham diet study Diet and the regulation of serum cholesterol in The Framingham Study An Epidemiological Investigation of Cardiovascular Disease Kannel W B Gordon T ed Washington D Government Printing Office

H A McDonough J H Newfeld H N Riss E M and Green J J Serum cholesterol Its distribution and association with dietary and other variables of 1000 men Isr J Med. Sci 5 111

Marr J W Heady J A Mills G L and R E Diet and plasma cholesterol in 99 Br Med J 1 571 1963

Pearce M L Hashimoto S Dixon W J A controlled clinical trial of a diet saturated fat in preventing complications of Circulation 40 (Suppl II) 1 1969

The effect of plasma cholesterol lowering diet survivors of myocardial infarction A controlled Acta Med Scand 466 (Suppl) 5 1966

berg H Olefsky J M Kimmerling C Crapo P Reaven G M Induction of hypertriglyceridemia by diet J Clin Endocrinol Metab 42 729 19 6

Glueck C J and Connor W E Diet coronary heart disease relationships reconnoitered Am J Clin Nutr 31 19 8

Ashley F J Jr and Kannel W B Relation of weight change to changes in atherogenic traits The Framingham Study J Chron Dis 27 103 19 4

14 Hulley S B Cohen R and Widdowson G Plasma high density lipoprotein cholesterol levels J A M A 238 2269 1977

15 Shepherd J Packard C J Patsch J R., Wallace R B *Malinow M R and Casdorph H R Effects of dietary* polyunsaturated and saturated fat on properties of high density lipoproteins and metabolism of apolipoprotein A I J Clin Invest 61 1 82 1978

16 Shepherd J., Packard C J Grundy S M Yeshurum D Gotto A M Jr and Taunton O D J Lipid Res 21 91 1980

17 Hartung G H Foreyt J P Mitchell R Vlasek I and Gotto A M Jr Relation of diet to high density lipoprotein cholesterol in middle aged marathon runners joggers and inactive men N Engl J Med 302 357 1980

18 Spritz N Review of the evidence linking alcohol consumption with liver disease and atherosclerotic disease Am J Clin Nutr 32(Suppl) 2731 19

Table IV Cost of routine investigations in patients already diagnosed on basis of history and examination

	Total no of patients	*No of patients diagnosed*	*Cost of routine investigations in diagnosed patients (£)*
Cardiovascular	276	257	3 107.38
Neurological	119	89	1 101 82
Endocrine	65	31	383 78
Alimentary	52	14	173 32
Respiratory	36	25	309 50
Urinary	19	12	148 56
Miscellaneous	63	34	420 92
Total cost in the two year study			£ 5 645 28
Cost per year			£ 2 822 64

In the follow up questionnaire to the family physician on the original hospital diagnosis in 548 patients there was a 60% response and the overwhelming majority of the answers confirmed the original diagnosis.

The cost of the routine investigations in those patients already diagnosed on the basis of the history and the examination is shown in Table IV The annual cost in the Medical Clinic was £2,823 (approx $6,500 U.S) A small survey among 28 physicians in the Trent Region to discover how many carried out routine investigations in their new outpatients similar to the procedure in the present study showed that 43[illegible] did so If this pattern was reflected nationally among the 1 044 hospital physicians employed in the N H S the total annual cost to the N H S of these useless investigations would be £ 1 26[illegible] 083 (almost 3 million dollars U S)

The study has clearly shown the major importance of the history in deciding the diagnosis and management of 630 medical outpatients. These findings support the views expressed by Platt on the vital importance of the history in clinical medicine Similar findings were also reported by Hampton and associates in a more limited study of 120 medical outpatients Clinical examination contributed much less diagnostic help its main benefits being confined to cardiovascular problems in the detection of hypertension and valvular heart disease and in respiratory problems in indicating chronic bronchitis and emphysema Similar results emerged in relation to the major value of the history in patient management with much less help provided by examination findings.

Routine blood count erythrocyte sedimentation rate blood urea and serum electrolyte estimations were of primary diagnostic help in only 1 [illegible] of patients [illegible] ver all Routine urine examination and blood sugar estimations also contributed little to diagnosis apart from [illegible] patients Chest radiographs were slightly more help[illegible] atory and cardiovascular problem [illegible] was th[illegible] gram in cardiovascular problems. N vert[illegible] nd blood sugar estimations in diabe[illegible] radiographs and electrocardiograms in respiratory and cardiovascular problems are hardly "routine" since they are specifically orientated to these problems.

The special investigations were of more value in diagnosis and management. The most useful were barium meals and cholecystograms, which decided most of the alimentary diagnostic problems. Thyroid function tests and glucose tolerance tests were also of considerable help in the appropriate endocrine disorder The exercise electrocardiogram contributed little in cardiovascular problems and the electroencephalogram was also of minor value in neurological problems.

What are the implications of the present study? First and foremost is guidance on the educational requirements of medical students Conventional training is based on a combination of history and examination findings before the diagnosis is considered A similar system is widespread in published case presentations in medical journals Much greater emphasis should be placed on the diagnostic and management value of the history Students and postgraduates should be well trained in taking a good history and in drawing diagnostic conclusions from the history before embarking on the examination This will encourage the student to seek specific examination findings to confirm or refute the diagnosis based on the history The traditional case presentation of history and examination followed by differential diagnosis should be changed to history differential diagnosis, and relevant examination findings A similar approach could be encouraged in medical journals and textbooks where inadequate emphasis on the importance of the history is often all too evident.

The study has also shown clearly the limited value of routine blood investigations Some doctors may carry out these routine investigations because they think it makes their approach more scientific others, perhaps, because they fear they might miss some other serious coexistent condition yet others may consider it desirable to have baseline measurements of these parameters to compare with possible future disorders Emphasis on the scientific investigational approach, however commendable though this may appear could lead to unselective application of laboratory investigations and minimize the importance of good history taking in diagnosis and management The value of the routine blood and urine investigations in the present study in showing unsuspected significant coexisting disease was small only 9.5[illegible] of patients. A similar limited incidence of unexpected abnormal routine laboratory results was also reported by Bredd in his study of 200 medical outpatients

Another important consideration is the cost of unnecessary routine investigations. In the Barnsley District General Hospital alone an annual saving of £2,823 ($6,500) could have been achieved in one medical clinic by omitting routine investigations in patients in whom the diagnosis had already been made on the basis of the history and clinical examination, and if the national picture followed the pattern of the local survey carried out in the Trent Region an annual total of over £1[illegible] million could have been saved

The justification for any investigation should surely be to answer a specific clinical question relating to diagnosis and management only when there is doubt as to either or to measure the effect of treatment that cannot be assessed on symptoms or signs alone Where these requirements are not operative however and where the result of the in[illegible]

Table I Diagnostic value of history, examination, and investigations

Referral diagnosis	No. of patients	History	Examination	Investigations	
				Routine	Special
Cardiovascular	276	[illegible]	[illegible]	[illegible]	
Neurological	119	[illegible]	1[illegible]		14
Endocrine	6[illegible]	[illegible]	1	11[illegible]	42[illegible]
Alimentary	52	2[illegible]			[illegible]
Respiratory	36	4[illegible]	[illegible]	1[illegible]	1[illegible]
Urinary	19	[illegible]	1	[illegible]	[illegible]
Miscellaneous	63	4[illegible]		[illegible]	[illegible]
Totals	630	[illegible]	[illegible]		1

Table II Management value of history, examination, and investigations

Referral diagnosis	No. of patients	History	Examination	Investigations	
				Routine	Special
Cardiovascular	276	[illegible]		4[illegible]	1[illegible]
Neurological	119	[illegible]		3[illegible]	21[illegible]
Endocrine	6[illegible]	11		[illegible]	[illegible]
Alimentary	5[illegible]	1[illegible]		[illegible]	[illegible]
Respiratory	[illegible]	[illegible]		1[illegible]	1[illegible]
Urinary	19	[illegible]		[illegible]	4[illegible]
Miscellaneous	63	44		11[illegible]	[illegible]
Totals	630	4[illegible]	—	[illegible]	24[illegible]

Table III Incidence of abnormal routine investigations and relevance to diagnosis

	No. done	Hb/WCC		ESR		[illegible]		[illegible]		Sugar		Chest radiograph		ECG	
		1	2*	1	2	1	2	1	2	1	2	1	2	1	2
Cardiovascular	276	1	9	2	1	0			6	0	1	[illegible]1	[illegible]	6[illegible]	16
Neurological	119	0	4	0	1	0	3	[illegible]	1	0	1	0	10	2	[illegible]
Endocrine	6[illegible]	0	3	0	1	1	[illegible]	0	4	1	0	–	–	2	–
Alimentary	5[illegible]	0	1	0	0	0	0	0	1	0	1	0		1	
Respiratory	36	1	0	2	0	0	3	0	4	0	0	–	3	3	4
Urinary	19	0	1	1	0	3	0	0	0	0	1	0	0	0	0
Miscellaneous	63	4	1	1	0	0	2	–	1	0	0	0	6	1	4
Totals	6[illegible]0	6 (1%)	19 ([illegible]%)	6 (1%)	3 (0[illegible])	1 (2%)	1 ([illegible])	8 (1%)	19 (3%)	21 (3%)	4 (1%)	[illegible]0 ([illegible]%)	62 (10%)	[illegible]5 (12%)	4[illegible] ([illegible]%)

* Primary condition for which patient was referred.
† Unexpected co-existent but clinically significant condition.

[illegible] diagnostic help in even less. The most useful routine tests were the chest radiograph and electrocardiogram but even they were of primary diagnostic help in only 5% and 12% respectively.

The diagnostic value of the more specific special investigations was greater. A positive test occurred most often with the [illegible]ogram in respiratory problems, but even then it decided the diagnosis in only [illegible]%. The glucose tolerance test was of the greatest diagnostic value of all the special tests, diagnosing [illegible]0% of the diabetic problems. Barium meal tests and cholecystography contributed substantially to the diagnosis of alimentary problems. The electroencephalogram, though often positive, decided the diagnosis in only 16% of cases; echoencephalogram and brain scan were of no value. Thyroid function tests were of considerable diagnostic value. [illegible] exercise test was of negligible diagnostic help in chest pain.

Table I Conditions where ASH is reported to occur

Condition	*No of cases/ Total cases*	*% of cases*
Acromegaly	8/9	88
Malignant hypertension	14/30	46
Chronic renal failure	7/23	30
Systemic hypertension	12/40	30
Systemic hypertension	3/30	10
Systemic hypertension	9/234	4
Mitral valve prolapse	16/190	8
Aortic valve disease	5/59	8 5
Mitral valve disease	2/36	5 5
Aortic & mitral valve disease	3/37	8 1
Coronary artery disease	4/79	5
Miscellaneous cardiac diseases	8/100	8
Miscellaneous cardiac diseases	40/100	40
Aortic stenosis & bicuspid valves	5	—
Weight lifters	14/14	100
Athletes	4/10	40
Normal subjects	5/10	50

In ludes patients with posterior infarction and congenital heart disease

show patients in whom the septum and posterior wall are of equal thickness There are only four echocardiograms which claim to show ASH and the interpretation of some of these is questionable While we do not deny that ASH can occasionally occur in conditions other than IHSS it is in our experience an infrequent finding Therefore rather than report our own experience (which might be open to dispute) we reviewed the left ventricular echocardiograms published in widely available echocardiographic textbooks and in current cardiology journals These contained numerous high quality echocardiograms from patients with those conditions listed in the table in which the thickness of the septum and posterior wall could be confidently measured We found no examples of ASH but on the contrary in all cases the thickness of the septum and posterior left ventricular wall were found to be remarkably similar

There are several technical problems and pitfalls in the correct identification of right and left ventricular endocardial surfaces This is essential for the measurement of septal and posterior wall thickness and relatively small errors can lead to an incorrect diagnosis of ASH For example it is easy to confuse [illegible] tricuspid valve chordae or papillary [illegible] right ventricular septal endocardium [illegible] thickness Over estimation of septal thickness [illegible] incorrect angulation of the [illegible] by beam width artefact [illegible] recent surveys has shown [illegible] others 20 measure septal thickness [illegible] mitral observer error [illegible]

In view of the [illegible] septal and posterior wall [illegible] published echocardiograms [illegible] conditions other than IHSS [illegible] ASH in [illegible] right ventricular hypertrophy the question arises as to whether some of the cases of ASH in these reports are erroneous The sceptical reader may be justified in not accepting a significant association between ASH and the conditions listed in the table until he is able to measure for himself in such reports echocardiograms clearly demonstrating ASH Because space in any publication is limited composite illustrations containing echocardiograms from several patients with no more than one cardiac cycle from each could be provided

D R Ramsdale B.Sc M.B CH.B MRCP
D H Bennett MD MRCP
Regional Cardiac Unit
Wythenshawe Hospital
Manchester M23 9LT
England

REFERENCES

1 Henry W L Clark C E and Epstein S E Asymmetric septal hypertrophy (ASH) Echocardiographic identification of the pathognomonic anatomic abnormality of IHSS Circulation 47 225 1973
2 Stern A Kessler K M Hammer W J Kreulen T H and Spann J F Septal free wall disproportion in inferior infarction The echocardiographic differentiation from hypertrophic cardiomyopathy Circulation 58 1978
3 Goodman D J Harrison D C and Popp R L Echocardiographic features of primary pulmonary hypertension Am J Cardiol 33 438 1974
4 Larter E W Allen H D Sahn D J and Goldberg S J The asymmetrically hypertrophied septum Further differentiation of its causes Circulation 53 19 1976
5 Hearne J M Sherber S H and Deleon C A Asymmetric septal hypertrophy in acromegaly—an echocardiographic study Circulation 51 and 52 II 1975
6 Criley J M Blaufuss A H and Abbasi A S obstructive IHSS Circulation 52 963 1975
7 Abbasi A S Slaughter J C and Allen M W Asymmetric septal hypertrophy in chronic haemodialysis patients (Abs) Circulation 53 and 54 II 190 1976
8 Toshima H Koga Y Yoshioka H Akiyoshi T and Kimura N Echocardiographic classification of hypertensive heart disease A correlative study with clinical features Jpn Heart J 16 3 1975
9 Dunn G F Chandraratna P D Carvalho J C E Basta L L and Frohlich F D Pathophysiologic assessment of hypertensive heart disease with echocardiography Am J Cardiol 39 789 19
10 Savage D D Drayer J M J Henry W L Mathews E C Ware J H Gardin J M Cohen E R Epstein S E and Laragh J H Echocardiographic assessment of cardiac anatomy and function in hypertensive subjects Circulation 59 4 623 1979
11 Chandraratna P A N Tolentino A O Mutucumarana W and Gomez Lopez A Echocardiographic observations on the association between mitral valve prolapse and asymmetric septal hypertrophy Circulation 55 1977
12 Maron B J Clark C E Henry W L Fukuda T and Edwards J E Mathews E C Redwood D R and Epstein S E Prevalence and characteristics of disproportionate ventricular septal thickening in patients with acquired or congenital heart disease Echocardiographic and morphologic findings Circulation 55 1 1977
13 Maron B J Savage D D Clark C E Henry W L Vlodaver Z Edwards J E and Epstein S E

whether positive or negative is unlikely to change either the diagnosis or management of the patient, there can be h tle justification in a king for it.

Gerald Sandler M.D
Consultant Physician
Dept. of Medicine
District General Hospital
Barnsley England

REFERENCES

1. Fa R. Two essays on the practice of medicine Manch Med Ga 27 13) 194
2. Hamm n J R. et al Relat e contribut ons of history taking, phys al examination and labora ry investigation to r ... and management of medical outpa tien B Med J 2 4 197
3. Brod J The rational basis of diagnosis in internal med J R Coll Physicians London 11 1977

Of saphenous vein arteriosclerosis

The saphenous vein *in situ* never develops art rios rotic changes. It can develop phlebosclerosis if there are varicose veins or an arteriovenous shunt in the area. But, if a segment of the vein is used for coronary artery bypass surgery t develops arteriosclerosis.[1] Why there and not in the leg? It must be due to the intraluminal pressure of the venous segment when it is used for the aorta-coronary shun and the trauma to the venous segment associated with its isolation and transplantation. The exposure to tobacco diet blood substances etc., is the same and is present for all veins as well as for all arteries As pointed out previously intra arterial pressure and now high intravenous pressure in the venous segment, is an important factor in the production of arteriosclerosis. Arteriosclerosis can be due in part to the anatomic and other disturbances associated with the system related to removal and transplantation of the venous segment. The areas of trauma can provide the nidus for the "arteriosclero sis to develop. The beating heart and the chroni adhesive pericarditis associated with venous aorta-coronary bypass must produce further physical trauma to the saphenous ven us segmen as the heart moves abou during each heart beat This could be an additional factor which contributes etiologically to the production of arteriosclerosis in the venous segment A s udy of such a venous bypass segment could contribute to understanding the pathogenesis of arteriosclerosis.

George E. Burch M.D
Tulane University S hool of Medicine
and Charity Hospital of Louisiana
New Orleans La.

REFERENCES

1. Grondin, C M., Campeau, L., Lesperance J., Solymoss, B. C., Vouhe P., Castonguay Y R., Meere C., and Bourassa, M. G. Atherosclerotic changes in coronary vein grafts six years after operation. Angiographic aspect in 110 patients J Thorac Cardiovasc. Surg 77 4 1979
2. Burch, G E., and Phillips J H. Hypertension and arteriosclerosis Am Heart J 60:163, 1960

Asymmetric septal hypertrophy in conditions other than IHSS

Since asymmetric septal hypertrophy (ASH) was first demonstrated by echocardiography in patients with idiopathic subaortic stenosis (IHSS) and in some of their first-degree relatives it has been reported in many other conditions These conditions can be divided into two groups. First, there are those disorders where the interventricular septum might be expected to be thicker than the posterior left ventricular wall—i.e., inferior myocardial infarction and right ventricular hypertrophy—whether due to primary pulmonary h perten sion or to congenital heart disease Secondly there are a large number of conditions where the presence of ASH could not be anticipated (Table I) It is the purpose of this Annotation to draw a tention to the contrast between on the one hand, the plethora of reports of ASH in this latter group and, on the other the paucity of published echocardiograms supporting them.

Only some of the publications l ed in the table are illustrated by echocardiograms, and curiou y most of these

neurons involved The consequence will be overeating Many obese people are compulsive eaters and their cravings for food are often uncontrollable Their condition has been described as carbohydrate addiction We think that the resemblances to narcotic addiction support our proposal of a common opioid mechanism Considering the unpleasant mental symptoms during withdrawal from morphine addiction it would be surprising if there were not some psychological symptoms associated with autoaddiction

Eating between meals

Enkephalin differs from morphine in its short half life less than a minute so as soon as the food leaves the duodenum there will be a rapid disappearance of enkephalin from the environs of the receptor neuron This contrasts with the relatively slow removal of morphine from the circulation This disappearance of enkephalin about a couple of hours after a meal will cause excessive activity in dependent neurons and will constitute a withdrawal syndrome before the next meal is due Eating snacks between meals will abate the consequent cravings for food and of course eating between meals is a common feature in obesity

Sugar

It is a general observation that sugar has a special relationship to appetite and to satiety We can for example eat a sweet when we are already replete with the savoury meat and vegetable course Sugar must have been a rare item in the diet of preagricultural man and the evolution of the satiety system must have taken place with a relatively sugar free duodenum In the intracellular digestive assay for the estimation of calorific value the direct diffusion of sugars into the cell might well swamp the process With an average daily consumption of about 130 g of sugar the sweet products of modern food technology may result in many people today being unable naturally and unconsciously to regulate their food intake

In conclusion if we are not all to be in a perpetual state of addiction the maximum enkephalin released by the sensory cells must not regularly exceed the amount required to ... the activity of the receptor neurons While the system ... cope with episodic excess chronic excess of enkephalin ... be pathological, and even a small regular excess would lead ... some degree of autoaddiction

R F McCloy FRCS
General H...
Northampton ...
Eng...
James McCloy DFC BSc
82 Wood Lea
London ...

REFERENCES

1 Stein L and Belluzzi J B Brain endorphins and ... sense of well being a psychobiological hypothesis ... Advances in Biochemical Psychopharmacology Costa E, and Trabucchi M eds New York 19.. Raven Press Vol 18 p 299
2 McCloy J and McCloy R F Enkephalins, hunger ... obesity Lancet 2 156 19.9
3 Liebling D S Eisner J D Gibbs J and Smith G P Intestinal satiety in rats J Comp Physiol Psychol 89 99.. 19..
4 Hunt J N and Stubbs D F The volume and energy content of meals as determinants of gastric emptying J Physiol 245 ..09 19..
5 Polak J M Sullivan S N Buchan A M J et al Endorphins in Gut Hormones Bloom S R ed Edinburgh 1978 Churchill Livingstone p ...
6 Fujita T and Kobayashi S Paraneuronal cells in the G E P endocrine system in Gut Hormones, Bloom S R ed Edinburgh 1978 Churchill Livingstone p ...
7 Collier H O J Consequences of interaction between opioid and receptor Biochemical Society Transactions 5 ..0 197..
8 Craddock D Obesity and its Management London 1978 Churchill Livingstone p 60

Effect of oral disopyramide on serum digoxin levels A prospective study

Recent pu... the con... increased se... is intoxicati... with propert... fore we studied ... serum digoxin le... ...tients receiving digitalis ...quinidine may lead to ...development of digital ...antiarrhythmic drug ...quinidine There- ...disopyramide on

Ten patients w... nous are given in ... (1) stable cardiac ... intake of digoxin ... and ... and (4) no ... ...rrhythmias diag... ...lowing criteria ...and time of ...te ... ...tion digoxin

levels In all patients digoxin levels were determined ... Tuesday and Friday at the same time interval after d... administration Then oral disopyramide was given for ... weeks in doses individually ranging from three to six ... daily Both digoxin and disopyramide levels were det... on Tuesday and Friday of the third week of the ... comparable time intervals to the first week ... lyses were performed using the paired t test

As shown in Table I prior to disopyramide administration serum digoxin levels varied from 0.8 to 1.5 (mean 1.1 ng/cc In the same patient the digoxin levels varied ... 0.4 (mean 0.17) ng/cc During disopyramide the ...

lence and characteristics of disproportionate ventricular septal thickening in patients with coronary artery disease Circulation 57 250 1978
14. Tencate J F Hugenholtz G P Van Dorp G W, and Roelandt J Prevalence of diagnostic abnormalities in patients with genetically transmitted asymmetric septal hypertrophy Am J Cardiol 43 731 1979
15. Gibson D G Traill T A Hall R J C and Brown D J Echocardiographic features of secondary left ventricular hypertrophy Br Heart J 41 54 1979
16. Feizi O and Emanuel R Echocardiographic spectrum of hypertrophic cardiomyopathy Br Heart J 37 1 86 1975
17. Menapace F J Hammer W J Kessler K K Ritzer T Bove A A, Warner H H and Spann J F Echocardiographic measurements of left ventricular wall thickness in weight lifters. A problem with the definition of ASH Am J Cardiol 39 2 6 19 7
18. Roeske W R, O Rourke R A Klein A Leopold G and Karliner J S Non invasive evaluation of ventricular hypertrophy in professional athletes, Circulation 53 2 6 1976
19. Feigenbaum, H Echocardiography Philadelphia 1976, Lea & Febiger
20. Roelandt J Practical echocardiography Oregon, 1977 Research Studies Press.
21. Chang S M mode Echocardiographic techniques and pattern recognition, Philadelphia 1976, Lea & Febiger
22. Sahn D J DeMaria A, Kisslo J, and Weyman, A Recommendations regarding quantitation in M mode echocardiography Results of a survey of echocardiographic measurements Circulation 58 1072, 197
23. Fowles, R E, Martin, R. P, and Popp R. L. Erroneous diagnosis of asymmetric septal hypertrophy due to an led interventricular septum Am J Cardiol. 43 34 19 9
24. Allen J W, Kim S J, Edmiston W A, and Venkataraman K. Problems in ultrasonic estimates of septal thickness Am J Cardiol 42 89 197

Autoaddiction a hypothesis on hunger and obesity

During the past ten years a group of some seven peptides with putative neurotransmitter and hormonal function have been found both in the brain and the gut One of these enkephalin has aroused special interest because it occupies the same receptor sites as morphine Experiments in the brain have shown that neuronal pathways, already firmly associated with the reduction of hunger drive are most probably part of an enkephalinergic system. Our proposal links this work with the enkephalin-containing cells in the gut to constitute a system which responds to the appropriate amount of food in the stomach by switching off eating It gives the sensation of satiety and the feeling of postprandial well being and leepiness. From a consideration of the opioid nature of the system we arrive at a feasible dysfunction by which a person can become addicted to his endogenous opiates a condition which we have called "autoaddiction "

Satiety

Experimental work has shown that satiety and cessation of feeding are elicited by samples of food from the stomach activating receptors in the wall of the duodenum We propose that enkephalin is a mediator In the gut enkephalin is found in the highest concentration in the antrum of the stomach and the duodenum, both in neurons and in open-ended secretory cells The enkephalin containing cell is probably a receptor secretory cell, sampling the contents of the duodenum at the open end of the cell and releasing enkephalin as a local hormone at the other We propose that the released enkephalin inhibits nearby afferent enkephalinergic neurons to switch off feeding and the hunger drive in the brain The strength of the reward depends on the number of secretory cells recruited by the influx of food into the duodenum The secretion of enkephalin from each can do no more than inhibit the activity of the neuron

Addiction

All the indications are that endogenous opiates are at least as addictive as morphine and we can see no good reason why the release of excess enkephalin should not be as addictive as circulating morphine We assume that addiction involves cellular changes as in the theory proposed by Collier in which opiates act by inhibiting the production of cyclic AMP and hence the activity of the neuron Continued inhibition leads to an increase in the capacity of the neuron to make more cyclic AMP and so it will need more opiate to suppress it (tolerance) The removal of the excess opiate unleashes the increased capacity to increase cyclic AMP and the resulting hyperactivity of the neuron is the cellular equivalent of the withdrawal syndrome

Autoaddiction and obesity

If for example the receptor-secretory cells in the duodenum overproduce and release too much enkephalin (or if the released enkephalin is not degraded with sufficient rapidity) then the regular excess of enkephalin over and above the amount required to reduce the activity of the receptor neuron will have the same effect as circulating morphine Repeated regularly after meals the excess enkephalin like uniform doses of morphine will soon cease to satisfy Tolerance/dependence will develop Some neurons cannot now be switched off by the released enkephalin and the satiety mechanism fails to an extent, depending on the numl

0002-8 03/80/1200 3 + 02$00 20 0 © 1980 The C V Mos

ity may be responsible[2] recent reports have indicated the possible causative role of the renin angiotensin system in the generation of the increased peripheral vascular resistance

Increased levels of plasma renin and plasma renin activity have been reported during conventional CPB Increase in the plasma level of angiotensin I has also been reported In a previous study the author and his colleagues have demonstrated a marked rise in plasma angiotensin II (AII) levels during nonpulsatile CPB with persistence of these elevated levels for around two to four hours postoperatively These elevated levels of plasma AII are significantly greater than those found during or after major non bypass procedures Elevation in the plasma level of angiotensin II during and after the period of CPB might therefore be considered likely to be of significance in the development of increased levels of peripheral vascular resistance

In view of this possible association between increased plasma AII levels and increase in vascular resistance 12 consecutive patients who had submitted to elective open heart surgical procedures were studied Six patients had prosthetic valve replacement procedures and six had coronary artery bypass grafting The mean age of the patients was 52 years There were seven males and five females Conventional nonpulsatile CPB was used in all cases with a bubble oxygenator The pump flow was calculated according to the standard formula

$$\text{Flow} = 2\,4\ \text{L/m} \quad \text{min}$$

The mean total bypass time was 92 3 minutes the mean temperature during perfusion was 35.5 C and the mean packed cell volume during bypass was 25%

In each patient blood samples for plasma angiotensin II estimations were obtained on full pump flow at the onset of total CPB and on full pump flow at the end of total CPB At these times measurements were obtained allowing the calculation of peripheral vascular resistance index Peripheral vascular resistance index (PVRI) was calculated according to the formula

$$\text{PVRI} = \frac{\text{mean arterial blood pressure} - \text{CVP}}{\text{cardiac index}}$$

Plasma angiotensin II levels were measured by the standard radioimmunoassay method In each of the 12 patients studied PVRI rose during CPB from a mean level of 20 87 ± 1.21 SEM to an end CPB level of 27.83 ± 1 61 SEM The mean rise in PVRI during bypass was 6 96 index units In percentage terms this is an increase in vascular resistance of 33.35% Similarly plasma angiotensin II levels rose during bypass from a mean level of 78 pg/ml ± 1 6 SEM to a mean end bypass level of 231 pg/ml ± 778 SEM (normal plasma AII level = < 35 pg/ml) The rise in plasma angiotensin II levels was correlated with the rise in peripheral vascular resistance index levels for each of the 12 patients The correlation coefficient obtained (r) was 0 91 This indicates a highly significant correlation between the quantitative change in plasma angiotensin II levels and the quantitative rise in peripheral vascular resistance index ($p < 0\,001$)

This study lends support to the concept that activation of the renin angiotensin system during conventional nonpulsatile CPB with the consequent elevation in the plasma level of angiotensin II may be a significant factor in the development of increased vasoconstriction during and after open heart surgical procedures If this is indeed so there are important therapeutic considerations regarding the management of the vasoconstriction It is increasingly recognized that reduction in elevated levels of vascular resistance is beneficial in the majority of patients in the early period after open heart surgery Several authors have recently demonstrated significant improvement in hemodynamic status in patients after open heart surgery who received vasodilator therapy for example with nitroprusside This benefit was considered to reflect improvement in left ventricular performance If angiotensin II is of major etiological significance in post-bypass vasoconstriction specific therapy designed to counteract the vasoconstrictive effect of angiotensin II would offer at least theoretical advantages over nonspecific vasodilator therapy particularly in relation to the known physiological effect of angiotensin II in producing increased subendocardial ischemia Specific anti AII therapy therefore offers a possible therapeutic superiority over current therapies (e g nitroprusside) in blocking the coronary vasoconstrictor effect of angiotensin II in addition to reducing elevated vascular resistance levels

In this regard recent reports using angiotensin converting enzyme inhibitor substance have suggested that such theoretical advantages of specific anti AII therapy may in fact be evident in clinical practice If however we continue to hold the maxim that prevention is better than cure attention ought also to be directed towards the prevention of the excessive activation of the renin angiotension system by modifying cardiopulmonary bypass perfusion The use of pulsatile flow during CPB is widely reported in the literature to be associated with significantly lower levels of vascular resistance compared to conventional nonpulsatile perfusion It may be that this hemodynamic effect of pulsatile CPB is achieved by means of reduced activation of the renin angiotensin system producing significantly lower levels of angiotensin II during the period of perfusion and in the early post bypass period

K M Taylor MD FRCS
W H Bain MD FRCS
J J Morton PhD
University Dept of Cardiac Surgery
Royal Infirmary
and the Medical Research Council
Blood Pressure Unit
Western Infirmary
Glasgow Scotland

REFERENCES

1 Estafanous F G Tarazi R C Viljoen J F and El Tawil M Y Systemic hypertension following myocardial revascularization Am Heart J 85 732, 1973
2 Hoar P F Hickey R F and Ullyot D J Systemic hypertension following myocardial revascularization J Thorac Cardiovasc Surg 71 859 1976
3 Turton M B and Matthews H R Catecholamines and peripheral vasoconstriction after open heart surgery Clin Chem Acta 50 419 1974
4 Hine I P, Wood W G Mainwaring Burton R W Butler M J Irving M H and Booker B The adrenergic response to surgery involving cardiopulmonary bypass as measured by plasma and urinary catecholamine concentrations Br J Anaesth 48 355 1976
5 Favre L Vallotton M B and Muller A F Relationship between plasma concentrations of angiotensin I

Table I Patient data

Patient no	Age	Sex	Diagnosis	Daily digoxin dose (mg)	Digoxin level (ng/cc) Before disopyramide		Digoxin level (ng/cc) After disopyramide		Daily disopyramide dose (mg)	Disopyramide level (mg/L)	
1	67	M	Old MI + VES	1/4	1 1	1	1 1	1 0	4 × 100	2 5	? 7
?	63	M	Parox A Fibr	1/4	0 8	0)	0 9	0 9	4 × 100	2 28	2.41
3	40	F	VES	1/4	1 0	0 8	0 8	0 7	4 × 100	2 62	2 03
4	43	M	CMP + VES	3/8	0 9	0 8	0 8	0 9	3 × 100	3 0	3 0
5	37	M	VES	1/2	1 1	1 0	1 0	1 6	3 × 200	2 43	2 45
6	54	F	Parox.A Fl	1/2	1 4	1 0	1 0	1 0	3 × 100	2 5	? 6
7	36	M	CMP + VES	1/2	1)	3	0)	1.2	3 × 200	2 5	2 3
8	48	F	VES	3/8	1 1		1 2	1 1	4 × 100	2.3	? 5
9	36	M	VES	3/8	1		1 1	1.2	3 × 200	2 8	3 0
10	62	M	Parox.A Fibr	1/4	1		1.2	1.2	4 × 100	2 4	2 5

Abbreviations MI = myocardial infarction VES = v ntri ular xt n x = pa oxysmal A = trial Fibr = fibrill t on Fl = flutter CMP = cardiomyopathy

digoxin levels ranged from 0 7 to 1 6 (mean 1 05 ± Differences in digoxin levels both per person an g oup before and during disopyramide administratio of statistically significant

Disopyramide levels varied from 2 3 to n 2.54 ± 0 26) mg/L which is considered to be in peutic range

We have to conclude that in patients on chronic ora therapy the concomitant administration of disopyram o not result in changes in serum digoxin levels

Hein J J Wellen M D
Anton P Gorgel M D
Simon J Bra M D
Frit W Bar M D
Edgar J Vanagt M D
Bob Phaf Ph D
Depts of Cardiology and Clini al Pharmacy
University of Limburg
Annadal Hospital
Maastri ht The Neth rland

REFERENCES

1. Ejvinsson G Effect of quinidine on plasma concentrations of digoxin Br Med J 1 2:9 19 8
2. Leahey E B Jr Reiffel J A Drusin R E Heissenbuttel R H Lovejoy W P and Bigger J T Jr Interaction between quinidine and digoxin J A M A 240 533 1976
3. Koch Weser J Disopyramide N Engl J Med 300 957 1979
4. Bigger J Th. Jr and Staruss, H C Digitalis intoxicity Drug interactions promoting toxi ity and the management of toxicity Semin Drug Treat 2 147 1972

The role of angiotensin II in the development of peripheral vasoconstriction during open-heart surgery*

Increased peripheral vasoconstriction is more commonly recognized during and after open heart surgical procedures using conventional techniques of cardiopulmonary bypass (CPB) Peripheral vascular resistance ing the period of perfusion and of the postoperative period Initial clinical characteristics of this synd no clear understanding of the While some reports have sugges

*This work was c rried ut with th d of gr t from the British Heart Foundation

neat and to lie with the hairline Cerebral blood flow and oxygen utilization increased The first patient of the series had a striking improvement in power Before the operation his right arm had been totally paralyzed for six weeks and within ten days of the procedure movement appeared first at the shoulder then at the elbow and finally at the wrist At the end of six weeks his arm movements were completely normal Three months later his inaccessibly stenosed internal carotid artery occluded and he suffered a recurrent completed stroke His deficit on this occasion was severe but the arm was relatively spared Most patients had a reduction in tone with improvement in power enabling an improvement in gait and stability

Psychological assessments were performed before and after operation in seven of the nine patients Improvement was claimed in six out of seven The left sided bypasses produced a striking improvement in verbal tests and intellectual improvement of one sort or another was demonstrable in all but one patient

The preliminary results suggest that extracranial to intracranial bypass may produce an improvement in some patients with longstanding moderate completed ischemic stroke As some of the patients in the report had a long standing total paralysis of the arm before surgery these deficits may have been regarded as too severe to fall within the criteria for entry into the Canadian cooperative study

R M Greenhalgh M.A M Chir F R C.S
Dept of Surgery
R D Illingworth F R C S
Dept of Neurosurgery
J McFie M.A M.D
Dept of Psychology
S P Mills B.A
Dept of Surgery
G D Perkin M R C P
Dept of Neurology
F Clifford Rose F R C P
Dept of Neurology
Charing Cross Hospital
Fulham Palace Road
London W6 8RF
England

REFERENCES

1 Jacobson J H, and Suarez E L Microsurgery anastomosis of small vessels, Surg Forum 11 243, 19
2 Donaghy R M P Patch and bypass in microangeonal surgery *in* Microvascular Surgery Donaghy R M and Yasargil M G eds Stuttgart 1967 Georg Thieme pp 75-86
3 Yasargil M C Anastomosis between the superficial temporal artery and a branch of the middle cerebral artery *in* Microsurgery Applied to Neurosurgery Stuttgart 1969 Georg Thieme pp 105 115
4 Leading Article Extracranial intracranial ana in the treatment of cerebrovascular ischaemia Br M J 2 9 1979
5 Leading Article Extracranial intracranial anastomosis Lancet 1 1384 1979
6 Greenhalgh R M Illingworth R D McFie J Mills P Perkin G D and Clifford Rose F Extracranial intracranial microrevascularisation for the treatment completed ischaemic stroke Br Med J 2 16, 1979
7 Greenhalgh R M and Illingworth R D Surgical technique for extracranial to intracranial bypass, Progress in Stroke Research I Greenhalgh, R M Clifford Rose F eds London 1979 Pitman M 393 403
8 McDowell F H The extracranial/intracranial study Stroke 8 545 1977

Of cardiac causalgia Horner s syndrome, and the cardiac dermatome

It is worthy of note that cardiac causalgia is practically limited to the left side of the chest wall left lung left side of the head and neck and left shoulder and left arm The left shoulder is regularly involved in this syndrome (postinfarct and postcardiotomy or Dressler syndromes) Rarely if ever is the right side of the body involved When cardiac causalgia major is present and the lungs are involved with "sterile" pneumonitis the pneumonitis is always in the left lung and rarely if ever in the right lung The hoarseness associated with cardiac causalgia has not been studied adequately I do not know if it is limited to the left vocal chord I have noted that some patients develop a typical *Horner s syndrome* as a manifestation of cardiac causalgia This syndrome has always involved the left eye and never the right eye It is usually of short duration

The distributions of these various manifestations of ca

0002 8703/80/120938 + 0 $00 20 0 © 1980 The C. V. Mosby

angiotensin II and plasma renin activity during cardiopulmonary bypass in man Eur J Clin Invest 4 13, 19 4

6. Roberts, A. J Niarchos A P Subramanian V A Abel R.M Herman S D Sealey Jean E Case D B White R. P Johnson G A Laragh J H and Gay W A Systemic hypertension associated with coronary artery bypass surgery predisposing factors hemodynamic characteristics, humoral profile and treatment J Thorac Cardiovasc Surg 74 6 197

7. Taylor K M Morton J J Brown J J Bain W H and Caves P K Hypertension and the renin angiotensin system following open heart surgery J Thorac Cardiovasc Surg 74 840 1977

8. Dusterdieck G and McElwee G Estimation of angiotensin II concentration in human plasma by radioimmunoassay Some applications to physiological and clinical states, Eur J Clin Invest 2 32 1971

9. Stinson, E. B Holloway E L, Derby G C., Copeland J G Oyer P E Beuhler D L and Griepp R B Control of myocardial performance early after open heart operations by vasodilator treatment J Thorac Cardiovasc Surg 73 523 1977

10. Kaplan J A and Jones, E. L Vasodilator therapy during [illegible] artery surgery Comparison of nitroglycerin [illegible] J Thorac Cardiovasc Surg 77 [illegible]

11. [illegible] D Brown J J Gray B Lever A F M [illegible] Medina A Morton J J and [illegible] Angiotensin and norepinephrine [illegible] experimental and clinical [illegible] man Am Heart J 89 321 1975

12. [illegible] J Morton J J Mittra S [illegible] Bain W H The haemodynamic [illegible] blockade after cardiopulmonary [illegible] J 41 [illegible] 197[illegible]

13. [illegible] A P Subramanian V A Abel [illegible] McCabe J C Case D B Laragh [illegible] W A Hypertension following coronary [illegible] graft surgery comparison of haemodynamic [illegible] nitroprusside phentolamine and con[illegible] inhibitor Circulation 58(Suppl 1) 43 [illegible]

14. Taylor K M Bain W H Russell M Brannan J J and Morton J J Peripheral vascular resistance and angiotensin II levels during pulsatile and non pulsatile cardiopulmonary bypass Thorax 34 594 1979

Extracranial to intracranial microrevascularization for the treatment of completed ischemic stroke

Extracranial surgery for internal carotid artery occlusion has had poor results, and attention has turned recently towards the possible improvement of cerebral blood flow by intracranial procedures Jacobson and Suarez first used the operating microscope for anastomosing small vessel and Donaghy reported seven human middle cerebral artery embolectomies using a T tube Yasargil and Donaghy then performed the first successful extracranial to intracranial bypass in man The end of the superficial temporal artery was anastomosed to the side of a cortical branch of the middle cerebral artery

There has been a recent interest in the British press following leading articles in the *British Medical Journal* and in the *Lancet* and a report of results of this procedure for the treatment of completed ischemic stroke

Extracranial to intracranial microrevascularization has been performed mainly for transient ischemic attacks prolonged reversible neurological deficit progressing stroke and much less commonly for completed stroke In Great Britain the procedure has not gained much popularity until recently The feeling among many clinicians there has been that most patients considered for the procedure were far too well to merit angiography and bypass surgery The procedure has recently become more popular and there has been less opposition to it for patients with completed ischemic stroke for whom nothing else could be offered

In the recent report completed strokes occurred between 1½ and 12 months (mean six months) before surgery The main deficits were weakness of the arm dysphasia intellectual deficit and to a lesser extent reduction in power in the leg All patients were alert and had some evidence of retained function in the affected hemisphere All patients had low density areas comparable with cerebral infarction on computerized axial tomography The deficits were stable at the time of surgery and were thought unlikely to show further spontaneous improvement A power record of the affected muscles an assessment of the speech deficit and regional cerebral blood flow estimations were performed and were repeated after the operation Psychological assessment was carried out before and after operation the tests were of intelligence verbal fluency (in the left sided cases) visual perception (in the right sided cases) and memory for both visual and verbal material

The operation was performed by a vascular surgeon with experience in microvascular surgery with the assistance of a neurosurgeon Using the operating microscope the end of the superficial temporal artery was anastomosed to the side of an appropriate cortical branch of the middle cerebral artery using interrupted 10/0 sutures

All nine of the anastomoses remained patent as assessed by arteriography or directional Doppler probe with a patent anastomosis it is possible to feel the pulsation of the superficial temporal artery All patients were alive and well at the time of writing and the procedure had an insignificant morbidity there was no skin flap sloughing and the scar proved to be

Letters to the Editor

Mitral prosthetic dehiscence and paraprosthetic regurgitation

To the Editor

In consequence of the case report by Chun and co workers concerning the Bjork Shiley mitral valvular dehiscence we would like to refer to our report of five patients with a Bjork Shiley mitral valve prosthesis and paraprosthetic regurgitation confirmed by cardiac catheterization left ventricular cineangiography and reoperation In four of these patients an abnormal anterior movement of the disc and the whole prosthesis, similar to that which Chun and associates described was found at the beginning of diastole in the echocardiogram. Other echocardiographic findings were an increased left atrial diameter compared with preoperative or previous postoperative measurement increased left ventricular end diastolic and stroke volumes and normal systolic posterior motion of the interventricular septum with a wide amplitude In two of these patients no murmurs were audible so that the paraprosthetic leakage may be insidious as previously described, and difficult to diagnose noninvasively without echocardiography In cardiac catheterization large v waves in the pulmonary capillary wedge tracings 30 to 60 mm Hg gradients across the mitral valve at the beginning of diastole and 20% to 50% mitral regurgitation fractions measured from quantitative left ventricular cineangiography were found in these patients Also the time from the aortic valve closure sound to the opening sound of the mitral prosthesis (A_2 MVO interval) in the phonocardiogram was abnormally shortened (60 ± 10 msec) suggesting increased left atrial pressure

Four patients were reoperated upon and in three of them the movement of the prosthesis in the echocardiogram was found to be normal after reoperation Left atrial diameter left ventricular end-diastolic and stroke volumes as well as the septal amplitude also decreased after successful reoperation In one patient in whose echocardiogram the movement of the prosthesis remained abnormal after reoperation a slight residual paraprosthetic leakage was found in a later catheterization study

Lately we have seen one more patient with paraprosthetic leakage confirmed by reoperation Abnormal movement of the prosthesis in the echocardiogram was found and we have never seen an abnormal prosthetic movement like this without paraprosthetic leakage The appearance and magnitude of this abnormal anterior movement of the prosthesis in the echocardiogram seems to depend on the position and magnitude of the detachment of the prosthesis from the mitral anulus as well as on the pressure gradient across the mitral valve at the beginning of diastole Because echocardiographic measurements in patients with normal prosthetic function did not change significantly after the first post perative month we recommend the initial postoperati e h cardiographic examination to take pla e up t the er d f the f rst postoperative month in every patient with a mitral al e prosthesis as a reference for later studies

Markku J Ikaheimo M.D
Cardiovascular Division Department of Medicine
Oulu University Central Hospital
SF 90220 Oulu 22 Finland

REFERENCES

1 Chun P K C Rajfer S I Donohue D J Bowen T E and Davia J E Bjork Shiley mitral valvular dehiscence AM HEART J 99 230 1980
2 Ikaheimo M J., and Takkunen J T Echocardiography after mitral valve replacement and criteria of ... thetic regurgitation Ann Clin Res 9 ... 19..
3 Rockoff S D Ross J Jr Oldham N N Mason D T Morrow A C and Braunwald E Ventricular regurgitation following prosthetic replacement of ... valve Am J Cardiol. 17 817 1966

Reply

To the Editor

We would like to thank Drs Ikaheimo and Takku ... bringing to our attention their article containing ... diographic illustration similar to ours of abnormal ... movement of the Bjork Shiley disk at the beginning ... diastole suggesting paraprosthetic mitral valve regurgitation It seems Bernal Ramirez and Phillips at the same ... published similar findings, referenced in our article Because ... the delay in SFDILINF Medline MFDLARS and I... Medicus cataloging articles, our literature search was ... able to turn up the latter article prior to our submitting ... article and its acceptance for publication The intent of ... article was not to report another case of the echocardiographic features of Bjork Shiley valvar dehiscence but to encourage the use of noninvasive tools *together in combination* to detect paraprosthetic leaks prior to catheterization The plain chest x ray and cinefluoroscopy as well ... diography are invaluable in its recognition In fact ... ing our echo strips we found what one *migh even suspect* be the intermittent appearance and disappearance *of por* ... of the prosthesis not previously illustrated (Figs 1 and 2)

Furthermore we would like to suggest another ... sive" procedure also done in the case we reported al... not exactly related to the patient s valvar dehiscence ... Swan Ganz catheter is already in position and the ca... acute pulmonary edema are entertained selective ... tions of pulmonary arterial branches and *hand injection*s ... Renograffin 76 may aid in excluding large pulmonary ... as a cause (see Fig 3)

In conclusion we strongly recommend pre and pos operative noninvasive studies and subsequent serial studies ... detection of prosthetic dysfunction We may thus hope... circumvent more serious complications from devel...

Patrick K C Chun M...
Sol J Ra...
Dennis J Donohue M...
Thomas E Bowen M...
James E Davia M...
Walter Reed Army Medical C...
Washington D C ...

REFERENCES

1 Ikaheimo M and Takkunen J Echocardiography ... mitral valve replacement and criteria of paraprosthetic regurgitation Ann Clin Res 8 ... 19..

causalgia are found within the same left dermatomes. The heart apparently is located within these dermatomes These clinical manifestations conform with studies in experimental animals and man which show the role of the left stellate sympathetic ganglion and the other sympathetic ganglia of the left side of the neck and upper thoracic region in neural regulation of cardiac function The mechanism for neurologic disturbances and location of the resultant manifestations needs careful study It is interesting though that the distribution of the clinical manifestations of cardiac causalgia within the body is limited to certain left dermatomes. This distribution is thought provoking. It is tempting to conjecture the possible clinical beneficial effects for patients with cardiac causalgia that might be expected from procaine blocking or resection of left stellate sympathetic and upper thoracic sympathetic ganglia

George E Burch M.D
Tulane University School of Medicine
and Charity Hospital of Louisiana
New Orleans La

REFERENCES

1 Burch G E Phillips J H and DePasquale N P Cardiac causalgia AM HEART J 76 725 1968
2. Burch G E and Giles T D Cardiac causalgia Arch. Intern Med 125 809 1970
3. Burch G E Cardiac causalgia and hoarseness AM HEART J 84 420 1972
4 Schwartz, P J Periti M and Malliani, A The long Q T syndrome AM HEART J 89 378 1975
5 Schwartz P J Brown, A M Malliani A and Zanchetti A (Eds.) Neural mechanisms in cardiac arrhythmias, New York 1978 Raven Press

type of cardiac arrhythmia for a brief period She then remained well until the age of 21 years (1979) when she died suddenly unrelated to exertion In neither case was there a family history of sudden death or heart disease but no clinical investigations were made of the other family members

Although these two cases may simply identify me as an extremely rare" cardiologist who has encountered sudden death in multiple patients with mitral valve prolapse I think the authors might well have downgraded their rating of sudden death prospects in this syndrome from "extremely rare" to "rare" or "uncommon Perhaps the auscultatory findings of mitral valve prolapse carry a less favorable prognosis when heard in childhood than when initially heard in the adult years.

Ray C Anderson M.D Ph.D
Professor of Pediatrics (Cardiology)
University of Minnesota
Pediatric Cardiology
Box 94 Mayo Memorial Bldg
420 Delaware Street S E
Minneapolis Minn 55455

REFERENCE

1 Leatham A and Brigden, W Mild mitral regurgitation and the mitral prolapse fiasco AM HEART J 99 659 1980

Reply

To the Editor

We thank Dr Anderson for his interesting letter suggesting that mitral valve prolapse might carry a less favorable prognosis in childhood We suppose that this is a possibility The incidence of mitral valve prolapse increases greatly with age suggesting a "wear and tear" effect superimposed on a minor congenital abnormality of the cusp and chordal tissue Maybe the valve abnormalities have to be more extreme to cause prolapse in children On the other hand sudden death, presumably from dysrhythmia would be unlikely in the absence of myocardial disease or a prolonged QT interval. One of Dr Anderson s patients did indeed have an abnormal electrocardiogram but there is no note of the QT interval. Dr Anderson does not tell us about the necropsy findings.

Aubrey Leatham
Wallace Brigden
National Heart Hospital
Westmoreland Street
London W1M 8BA
England

On rheumatic fever in children

To the Editor

I have read with interest the excellent review of Rheumatic fever in children by Disciascio and Taranta and congratulate the authors on their magnificent work The subject and its geographic importance are well covered The following comments, however are in order

The disease continues to be a [illegible] f morbidity and mortality in the "deve [illegible] ntries [illegible] world Among the factors affecting the higher incidence of the disease [illegible] these areas the most important in my opinion are th[illegible] unfavorable socioeconomic conditions. One would thus [illegible] to look at the whole spectrum of these conditions. Obvious[illegible] crowding in houses is a contributing factor so is the unava[illegible] ability of proper medical care etc But one often neglecte[illegible] aspect of the spectrum is nutrition Although there is [illegible] evidence of a predisposing dietary deficiency in adult life th[illegible] role of nutrition in the first six months of life in regard t[illegible] rheumatic fever has not yet been thoroughly investigated. I[illegible] my opinion there are some clues as to the possible role o[illegible] nutrition in the first year of life in rendering a pers[illegible] susceptible to rheumatic fever It has been shown tha[illegible] infantile malnutrition in the first six months of life leads to [illegible] imbalance of the immune system—i e B and T cell fa[illegible] and complement production Since autoimmune disea[illegible] are felt to result from such imbalances and rheumatic fever i[illegible] favored by many as an autoimmune disease one can [illegible] relate the two together and at least suggest that in th[illegible] economically deprived populations where infantile mal[illegible] tion is quite common genetically susceptible individuals cou[illegible] be hypersensitized by immune imbalance and thus become a[illegible] oversusceptible host Future exposure to rheumato[illegible] streptococci in such individuals would result in an attack o[illegible] rheumatic fever The possibility that some serotypes of strep[illegible] tococci in areas of high incidence are more rheumatogenic [illegible] suggested by a 57% M typability in 100 strains of group [illegible] beta hemolytic streptococci studies in an area of high inc[illegible] dence The observation that the disease is rather rare [illegible] the Egyptian countryside as opposed to Cairo where [illegible] population live under conditions of extreme crowd[illegible] similar to our observations in Iran We noted that over [illegible] patients suffering from severe rheumatic heart disease we[illegible] from urban and heavily populated areas and the majority ha[illegible] been born in these areas Thus, the exposure of immigra[illegible] unfamiliar serotypes is probably not always the case Ra[illegible] one would have to examine the factors created by crowd[illegible] such urban and overpopulated areas some of which probab[illegible] play a role in the pathogenesis of the disease Neverthele[illegible] is known that infantile malnutrition is more common in [illegible] communities than in rural areas where traditionally brea[illegible] feeding has continued to be practiced Thus studies of th[illegible] relation of nutrition in the first six months of life in makin[illegible] host more susceptible to environmentally triggered au[illegible] mune disease can open an avenue to the pathogenesis [illegible] rheumatic fever

Our experience with over 1 000 children with rheuma[illegible] heart disease showed that mitral stenosis was the second m[illegible] common cause of isolated rheumatic valvular le[illegible] accounting for more than 20% of the cases. In our series [illegible] have clearly distinguished between pure mitral s[illegible] those stenoses associated with mitral regurgitation All [illegible] children with severe mitral stenosis who underwent s[illegible] were felt to have rheumatic valves (either duri[illegible] surgery or [illegible] subsequent pathologic examination of the valves) a[illegible] about 60% a history of rheumatic fever was elicited. In [illegible] instance did the valve have the characteristics of conge[illegible] mitral stenosis If one strongly argues a viral etiolo[illegible] mitral stenosis If one strongly argues a viral etiology f[illegible] disease as previously suggested it will have to be a be[illegible] hemolytic sterptococcus-dependent virus otherwise [illegible] cases would have been observed elsewhere in the world

As suggested by the authors, the Jones [illegible] boundaries between disease and nondisease states. As p[illegible]

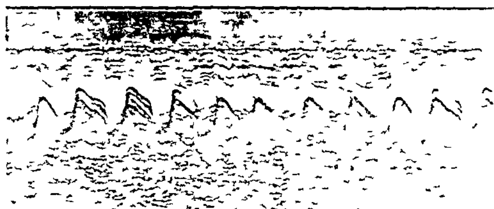


Fig 1 Echocardiographic tracing of prosthetic valve suggesting its displacement across the suture line

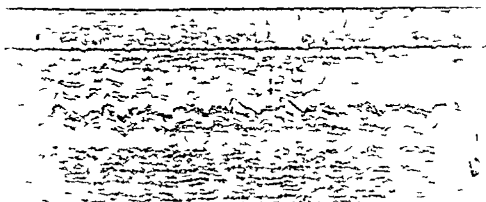


Fig 2 Another echocardiographic tracing illustrating a portion of the prosthesis appearing above the annulus



Fig 3 Chest x ray with selective injection of dye through a Swan-Ganz catheter into the right pulmonary arterial branches.

2. Bernal Ramirez J A and Phillips J H Echocardiographic study of malfunction of the Bjork Shiley prosthetic heart valve in the mitral position Am J Cardiol 40 449 1977

Idiopathic mitral valve prolapse and sudden death

To the Editor

In their review of mild mitral regurgitation and its most common cause mitral valve prolapse Leatham and Brigden conclude that sudden death is extremely rare Unfortunately this has not been my experience inasmuch as I have encountered two sudden deaths among the approximately 50 children in whom I have made a diagnosis of idiopathic mitral valve prolapse One was a girl whom I first examined at nine years of age eight months after her family physician had first heard a heart murmur on a routine examination Aside from the late systolic murmur and click the only finding of note on interval examinations over the years was a flattening or inversion of the T waves in Leads 2 and 3 She had no symptoms until the age of 21 years (1974) when she developed palpitations, confirmed as ventricular premature beats by electrocardiography Several days later and before any therapy had been started she died suddenly unrelated to exertion The second case was a girl who had a typical late systolic murmur and click when I first examined her at seven years of age two years after her family physician had noted an abnormal heart sound Her electrocardiogram remained normal over the years but at 19 years of age she had some